**EFFICACY AND SAFETY OF SUCROSE FOR PROCEDURAL PAIN RELIEF IN
PRETERM AND TERM NEONATES**

By

Sharon McDonald Gibbins

**A thesis submitted in conformity with the requirements
For the degree of Doctor of Philosophy
Graduate Department of Nursing Science
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ABSTRACT

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The purpose of the randomized controlled trial was to determine the most efficacious and safe method of sucrose administration for procedural pain relief in preterm and term neonates. The influence of gestational age on the safety and efficacy of sucrose was explored. The conceptual framework was based on the Gate Control Theory of Pain (Melzack & Wall, 1965; 1996) and an understanding of neonates' capacity to transmit, transduce, perceive and modulate pain impulses in light of their neurological development.

A sample of 190 neonates was obtained from one Neonatal Intensive Care Unit (NICU) in Metropolitan Toronto. The primary outcome, pain, was measured by the Premature Infant Pain Profile (PIPP) (Stevens, Johnston, Petryshen & Taddio, 1996). Safety was measured by established criteria for adverse events. Stratification for gestational age was used to control for the effects of age on the primary outcome. Parents of eligible neonates were approached during the first week of life and consent to participate in the study was sought. All neonates whose parents gave consent were randomized, using central randomization, to one of three intervention groups; sucrose and non-nutritive sucking (NNS), sucrose alone or water and NNS. Physiological and behavioral data were collected during the baseline, warming, lance, squeeze and return to baseline phases of a heel lance procedure performed to collect blood for standard diagnostic testing. Demographic data were collected from the medical and nursing records prior to randomization. Data analyses for the primary and exploratory questions were performed utilizing analyses of variance (ANOVA), and post hoc analyses for significant ANOVAs were used to determine where significant differences were found. Due to the small number of adverse

events, safety data were reported by frequencies. A hierarchical regression model was used to determine which variables contributed to the variance in pain scores.

There were statistically significant differences between intervention groups, with sucrose & NNS being most efficacious. Moreover, the differences in pain responses were significant within each gestational age stratum, with sucrose and NNS most efficacious in all groups. Although the results were statistically significant, further research to determine clinical significant differences in pain scores is required. Few adverse events ($n = 6$) occurred during the study period and none of the events occurred in the sucrose and NNS group. The most immature preterm neonates experienced the greatest number of adverse events compared to their older preterm and term counterparts. Intervention group and gender contributed to the most variance in pain scores. PIPP scores were significantly lower in the most immature gestational age stratum (27 – 31 6/7 weeks) compared to older preterm (32 – 35 6/7 weeks) and most mature ($\geq$ 36 weeks) neonates.

Sucrose and NNS are readily available in NICUs and easily incorporated into standard nursing care. The challenge will be to have nurses incorporate these research findings into practice. Since neonatal pain assessment and management is an ongoing requirement in the NICU, continuous evaluation of the best available practices is required. Therefore, future research examining the efficacy and safety of repeated doses of sucrose & NNS (with or without other interventions) for a variety of painful procedures and diseases is required.

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Chapter I

INTRODUCTION AND PROBLEM STATEMENT

Introduction

Approximately 6.8% of neonates in Canada are born preterm (36 weeks gestation or less) (Joseph et al., 1998). Over the past decade, the technological and pharmacological advances in Neonatal Intensive Care Units (NICUs) have increased the survival rates for preterm neonates (Philip, 1995). As more preterm and acutely ill neonates survive, more neonates will undergo painful tissue-damaging stimuli to improve their survival (Anand & Selanikio, 1996; Barker & Rutter, 1995; Johnston, Collinge, Henderson & Anand, 1998). Zahr and Balian (1995) found that neonates in NICUs are rarely left undisturbed, and 56% of their contacts were highly or moderately intrusive, involving nursing actions such as suctioning, chest physiotherapy, venipuncture and heel lance. Only 8.2% of the contacts with neonates in the NICU were found to be comforting contacts from nurses. Stevens, Johnston, Franck, Petryshen, Jack and Foster (1999) found that neonates born between 27 to 31 weeks gestation received a mean of 134 painful procedures within the first two weeks of life and approximately 10% of the youngest and/or sickest neonates received over 300 painful procedures. The consequences of multiple repeated painful procedures on clinical outcomes remain unclear.

The major approaches to pain management in neonates include pharmacological, environmental and behavioral interventions. Pharmacological interventions are usually reserved for severe pain and include agents, such as morphine, that have been used in adult medicine. The goal of pharmacological pain management is to alleviate pain with drugs that are safe and effective. A joint statement of the Fetus and Newborn Committee, Canadian Paediatric Society and The Committee of Fetus and Newborn, Committee on Drugs, Section on Anesthesiology and Section on Surgery, American Academy of Pediatrics has provided guidelines for pharmacological pain management in neonates (2000). The guidelines are not specific for the type of pain (e.g. chronic versus acute), nor do they recommend one drug over another. However, they do provide a framework for health professionals to prevent, limit or avoid painful procedures and provide analgesia.

Environmental, behavioral and pharmacological interventions have been evaluated for the management of pain in neonates. Franck (2000) makes a plea to health professionals not to just categorize interventions into broad classifications but to use correct terminology for the type of intervention employed. The use of terminology that classifies approaches into “pharmacological” and “non-pharmacological” implies that clinicians must choose between different treatment options for neonatal pain management, and this choice often contributes to sub-optimal pain management in neonates. Franck (1987) found that although most health care professionals employed in NICUs believed that analgesia was underused for neonates, there was a lack of consistency in both attitudes and practices among the surveyed health professionals. Bauchner, May and Coates (1992) reported that analgesics were used significantly more regularly in pediatric units than in neonatal units for many noxious stimuli such as lumbar punctures or chest tube insertions. In a comprehensive survey of 362 physicians, McLaughlin, Hull, Edwards, Cramer and Dewey (1993) evaluated the attitudes and practices of health

professionals providing pain management in neonates. Almost all of the physicians indicated that they thought even the most immature preterm neonates (<28 weeks gestation) were able to perceive pain. However, the use of analgesic agents for neonates was variable. Physicians who did not feel that neonates perceived pain were less likely to prescribe analgesics and more likely to state that the risk of addiction outweighed the benefits of pain reduction. Porter, Wolf and Miller (1999) surveyed 374 neonatal clinicians. Using a 5-point Likert scale, clinicians rated the painfulness of 12 commonly performed bedside nursery procedures such as nasogastric tube insertion, lumbar punctures or circumcision. The clinicians' ratings for the procedures were compared with the magnitude of the neonates' physiologic and behavioral responses to determine how closely they were correlated. There was a correlation between the clinicians' rating of painfulness and the magnitude of heart rate changes from baseline to procedure ($r = 0.25$, $p = 0.001$). However, gestational age affected clinicians' ratings of painfulness, with the most immature neonates rated as having the least degree of pain associated with similar procedures. The differences in clinicians' perceptions of pain, based on gestational age, predispose the most immature neonates to sub-optimal pain management.

Anand and Selanikio (1996) prospectively studied the analgesic and sedation practices in 109 NICUs. Demographic data and data on the use of analgesics or sedatives and side effects were collected for 1068 preterm neonates over a one-week period. Only post-operative pain was managed adequately. Procedural pain was not routinely treated with either pharmacological, behavioral or physical strategies. In a recent survey of 86 NICUs (Sabrine, Wilkinson, Robbins, Cleaver & Williams, 2000), analgesia was used less than 10% of the time for many invasive procedures including intravenous cannulations, venipunctures and lumbar punctures. For highly invasive procedures such as chest drain insertion, analgesia was used only 16% of the time. Twycross (2000) reported that although pediatric nurses believed that neonates experience pain,

they did not regard pain management as high of a priority as other aspects of their nursing role. Furthermore, the nurses cited lack of knowledge concerning pain assessment and management as contributing factors to the under-use of pain relieving interventions. By virtue of the (a) number of painful procedures undertaken in preterm neonates, (b) evidence to suggest that procedural pain is poorly managed and (c) concerns about the safety of pharmacological agents (e.g. side effects, tolerance) in neonates, environmental or behavioral approaches to neonatal pain management appear to be a feasible alternative for pain relief for commonly performed procedures. The administration of sucrose with and without nonnutritive sucking (NNS) on a pacifier has been examined in two systematic reviews (Stevens, Taddio, Ohlsson & Einarson; 1997; Stevens & Ohlsson, 1998). Although the reviews indicated that sucrose reduces the physiological (i.e. heart rate) and behavioral (i.e. cry duration) indicators of stress/pain in neonates following painful stimuli, there is inconsistency in the appropriate dose and route of administration.

Although there is evidence to support neonates' abilities to mount stress responses to tissue damaging stimuli and evidence for the use of sucrose for procedural pain relief in healthy neonates, the optimal method of sucrose administration to reduce procedural pain in acutely ill term and preterm neonates has not been adequately determined. In addition, there is little information about the efficacy of sucrose in neonates born at different gestational ages. These gaps in knowledge will be addressed by recruiting an adequate sample size and employing a valid multivariate measure of pain to determine the most efficacious and safe method of administering sucrose to neonates across gestational ages.

Chapter II

REVIEW OF THE LITERATURE AND CONCEPTUAL FRAMEWORK

In this chapter, pain (definitions, development and responses) and research evidence relevant to the management of procedural pain for neonates will be discussed. The Gate Control theory (GCT) and an understanding of neuroanatomy and neurochemistry will provide the conceptual rationale for the pain relieving interventions (sucrose and NNS) for procedural pain relief in preterm and term neonates.

Review of the Literature

Definition of Pain

The debate over the existence of pain in neonates has existed for decades (Anand & McGrath, 1993; Barr, 1992; Boreus, 1990; Craig & Grunau, 1993; Pokela, 1994). The controversies surrounding pain and its management in neonates have largely been based on personal practices, traditions, and lack of rigorous assessment to measure pain. The controversy over the existence of pain in neonates results, in part, from the interpretation of the most generally accepted definition of pain. Pain is defined by the International Association for the Study of Pain (IASP, 1979) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Neonates are not capable of verbal communication and must rely on others to make inferences from behavioral and physiologic indices for all of their physiological needs, including the assessment and management of pain.

New perspectives on the definition of pain challenge the IASP definition of pain to include living organisms that are incapable of self-report, such as newborns and older infants (Anand & Craig, 1996). Self-reports of pain suggest that an individual has perceived a stimulus to be painful, and he/she verbalizes the sensation as painful (Barr, 1992). Ideally, there should be congruence between perceiving pain and reporting pain. However, this congruency is often context dependent, and influenced by; (a) who is eliciting the self-report, (b) the methods used to assess pain, (c) the underlying reasons for eliciting the description of pain and (d) the

individuals' perception of the consequences of reporting pain. The inconsistency of self-reports often results in unreliable information and hence, the "gold standard" for pain assessment cannot be achieved (Anand & Craig, 1996).

The IASP definition of pain further suggests that pain is an emotion that must be learned through experience. Anand and Craig (1996) argue that the perception of pain is an inherent quality of life that serves to guard the individual against injury. Anand and Craig (1996) propose that neonates' behavioral responses to tissue-damaging stimuli are forms of self-report that should not be discounted but rather seen as the gold standard for pain measurement. Responses supporting Anand and Craig's (1996) arguments suggest that neonates' expressions of unpleasantness do not fit with the definition of pain and this contributes to the failure to recognize and treat pain aggressively. Efforts should be directed towards increasing recognition of pain and developing broader sources of information to infer the subjective experience of pain in nonverbal neonates (Derbyshire, 1999).

Historically, all neonates, and particularly preterm neonates, were viewed as incapable of pain perception because of an immature central nervous system (CNS). Neonates' responses to tissue-damaging stimuli were thought to be decorticate and the lack of myelination within the CNS prevented perception of pain (Andrews & Fitzgerald, 1994; Barr, 1992; Carlson, Clement & Nash, 1995; Carraccio, Feinberg, Hart, Quinn, King & Lichenstein, 1996; Grunau & Craig, 1987). Giannakouloupoulos, Sepulveda, Kourtis, Glover and Fisk (1994) examined fetus' responses to pain and found that hormonal stress responses in fetuses occur from 23 weeks gestation. Teixeira, Fogliani, Giannakouloupoulos, Glover and Fisk (1996) also reported that fetal blood flow to the brain is reduced during invasive procedures such as fetal surgery. The results of Giannakouloupoulos et al. (1994) and Teixeira et al. (1996) support the idea that preterm neonates are capable of mounting physiologic responses to noxious stimuli, although the expression of these responses in very preterm neonates may be somewhat limited or different than in older preterm neonates and term neonates (Fitzgerald, 2000).

Neurological Anatomy

Nociception.

Nociception refers to the detection of a noxious stimuli and the transmission of information concerning the stimuli to the brain for interpretation (McGrath, 1993). Unlike the concept of pain, nociception does not require verbal self-report. Therefore, the term 'nociception' provides a better description of neonates' responses to a tissue-damaging stimulus. Nociception involves both the nervous system, where pain signals are processed, and the endocrine system, where neuropeptides associated with pain transmission are generated.

The four basic processes of nociception include: (a) transduction; where noxious stimuli in the periphery are detected by primary afferent neurons, called nociceptors, (b) transmission; where movement of impulses from the site of transduction to the brain occurs, (c) perception; where recognizing, defining and responding to pain occur, and (d) modulation; where activation of descending pathways that exert inhibitory effects on pain transmission occurs (Paice, 1991). Nociception begins with a noxious stimulus that is detected by primary afferent neurons. The stimulus activates specific impulses that are conducted along the peripheral nerves that synapse in the dorsal horn of the spinal cord. Other tracts ascend from the spinal cord to the thalamus and other areas of the brain including the somatosensory cortex and the association cortex (Franck, Greenberg & Stevens, 2000). Two types of nociceptive fibers are responsible for the transmission of pain from the site of injury to the spinal cord, C-fibers and A-delta fibers. C-fibers are unmyelinated, small-diameter, slow conducting fibers that transmit poorly localized, dull aching pain. C-fibers respond to mechanical, thermal and chemical stimuli at approximately 2 meters per second. A-fibers are minimally myelinated, larger in diameter, and faster conducting fibers that transmit well localized, sharp, and pricking pain in 5 to 25 meters

per second. Unlike C-fibers, A-delta fibers are not sensitive to chemical stimuli (VanKeuren & Eland, 1997).

The nociceptive impulses terminate in the spinal cord where excitatory neurotransmitters, such as adenosine triphosphate, glutamate, neurokinin A and substance P, are released. These neurotransmitters continue to transmit the nociceptive impulse (Anand & Carr, 1989; Fitzgerald & Anand, 1993; Rang, Bevan & Dray, 1993; Paice, 1991). The n-methyl-D-aspartate (NMDA) receptors, derived from substance P and glutamate, are distributed throughout the spinal cord gray matter until 10 – 12 days after birth (Fitzgerald, 2000). The composition of NMDA receptors in the neonatal brain differs from adults, with increased expression in the cortex (Kim, Foy & Thompson, 1996) that is felt to be associated with increased vulnerability to excitotoxic damage in the newborn brain. NMDA receptors are thought to be responsible for the central sensitization or “wind-up phenomenon” where sensory inputs to the CNS are amplified, resulting in increased pain and changed neuronal circuitry (Cui, Meyerson & Lindeoth, 1999). This “wind-up”, hyperalgesic, state has been observed in both preterm and term neonates exposed to sequential painful procedures. Fitzgerald et al. (1989) found that preterm neonates exposed to daily painful procedures in the NICU had progressively lower sensory thresholds over the four-week study period. Pain responses were elicited with less invasive stimuli over consecutive days, thereby suggesting that hypersensitization had occurred. When application of lidocaine-prilocaine creams to the involved heel was used, no changes in sensory threshold were observed. In a similar study, Gunnar (1992) found that neonates who were exposed to frequent painful stimuli over two successive days, had greater pain responses on the second day. The differences in pain responses over time suggest that hypersensitivity in the area of previous tissue damage may

have occurred. These data further support the occurrence of sensitization in preterm neonates with repetitive painful stimuli.

From the spinal cord, transmission by second-order neurons to the brain stem and thalamic regions occur where pain impulses can be further distributed throughout the brain. Other areas are also believed to be involved with the interpretation of pain. The limbic system is believed to be responsible for the emotional and behavioral response to pain while the reticular system is believed to be responsible for the autonomic responses (Fields, 1987). Once pain transmission and perception occur, fibers in the spinothalamic tract stimulate regions of the midbrain that send descending projections to the dorsal horn to inhibit pain impulses. The descending fibers release substances such as endogenous opioids, serotonin, norepinephrine, γ -amino butyric acid (GABA), acetylcholine and neurotensin that have the ability to inhibit pain impulses. The dorsal horn also contains opiate receptors that may have a role in modulating pain. When opioids are administered or when the body's own endogenous opioids are released, they bind to the opiate receptors and inhibit the release of neuromediators that propagate the pain impulse. Knowledge of opiate receptors is essential for optimal pain relief.

In summary, the function of nociception is to provide information about a stimulus and to elicit a response from highly specialized fibers that indicate the location and intensity of the stimulus. Nociceptive neurons are sensitive to thermal, mechanical or chemical noxious stimuli, contain and release neuropeptides, and are sensitive to particular growth hormones that are involved in neurogenic inflammation (e.g. vasodilation, vascular leakage) and neuroimmune regulation (Rang et al., 1993). Nociceptive neurons also control smooth muscle contraction and glandular secretion into the gastrointestinal and urinary tracts (Anand & Carr, 1989). There is sufficient evidence to suggest that fetuses are capable of nociception by 20 – 24 weeks gestation. The fetal neuroanatomy, neurophysiology and neurochemical systems are sufficiently

developed to enable neonates of varying gestation to respond to tissue-damaging stimuli, although the responses of the most preterm neonates may be less well defined than those of preterm neonates of more advanced gestational age (Fitzgerald, 2000). The neural pathways for pain perception are present in newborn neonates and the density of nociceptive nerve endings in the skin of neonates is similar to or greater than that in adult skin (Anand, 1993; Anand & Hickey, 1987; Anand & Carr, 1989). The research supporting the neuroanatomy and neurochemistry of nociception in neonates is summarized in Table 1.

Table 1.

The Neuroanatomy and Neurochemistry of Nociception in Neonates

Gestational age	Neuroanatomy	Neurochemistry
6 th week	Development of synapses between sensory fibers and receptive neurons in the dorsal horn (Anand & Carr, 1989; Fitzgerald & Anand, 1993; Okado, 1981)	
7 th week	Cutaneous sensory perception appear in perioral area and are complete by the 20 th week. Reflex responses begin and spontaneous movement in the absence of external stimuli occur (Anand, 1993; Humphrey, 1964)	
8 th week	Fetal neocortex begins and by 20 weeks, the cortex has a full complement of 10^9 neurons (Anand & Carr, 1989)	Appearance of neuropeptides (somatostatin, prostaglandins) in the dorsal horn (Anand & Carr, 1989; Fitzgerald & Anand, 1993)
13-14 th week	Various types of cells in dorsal horn begins (complete by 30 weeks). (Anand, Phil & Carr, 1989; Fitzgerald, 1993a)	Enkephalin, GABA appear in the dorsal horn (Fitzgerald, 2000; Charnay et al., 1987)
16 th week	Dendritic processes of cortical neurons proliferate and develop synaptic targets for incoming thalamocortical fibers and intracortical connections (Anand & Carr, 1989; Anand et al., 1989)	Substance P appears in the dorsal horn (Anand and Hickey, 1987; Charnay et al., 1987; Marti et al., 1987)

Table 1.

The Neuroanatomy and Neurochemistry of Nociception in Neonates (continued).

Gestational age	Neuroanatomy	Neurochemistry
20 th week	Cortical hemisphere have full complement of neurons (Anand & Carr, 1989; Marin-Padilla, 1983)	<i>B</i> endorphins observed in anterior and intermediate lobes of the fetal pituitary gland (Begeot, Dubois & Dubois, 1978; Li, Dubois & Dubois, 1979)
22 nd week	Dendrites begin to develop and migrate towards synaptic targets. Functional maturity of cortex is demonstrated by fetal and neonatal EEG patterns that are evident by 22 weeks gestation and bilaterally synchronous by 27 weeks (Rakic & Goldman-Rakic, 1982)	
20-24 th week	Thalamocortical connections established and continue to synapse until 5 years post natal life	
30 th week	Nociceptive pathways to the brainstem and thalamus are myelinated. Well defined periods of sleep and wakefulness (Fitzgerald 1993)	
37 th week	Thalamocortical connections are myelinated	

Note. Adapted from Anand (1990), Paice (1991) and Stevens (1993).

Pain Responses

Physiological Responses

Neonates have the anatomical and functional requirements for mounting a physiological response to painful stimuli (Anand, 1990; Anand, Phil & Hickey, 1992; Fitzgerald, 1991; Fitzgerald & Anand, 1993; Anand & Hickey, 1987; Anand et al., 1992; Stevens & Johnston, 1994). These responses are evident in both term and preterm neonates. The systems modulating the perception of pain are closely coupled with the cardiovascular system (Randich & Maixner, 1984). Therefore, the most common physiological pain responses include those observed with the stress response: (a) increases in heart rate, respiratory rate and intracranial pressure, (b) decreases in vagal tone, oxygen saturation, and blood pressure and (c) autonomic changes such as changes in skin color, nausea, vomiting, palmar sweating and dilated pupils.

The hypothalamic-pituitary-adrenal (HPA) axis represents a regulatory system that modulates different types of stressors to maintain equilibrium within the endocrine, autonomic, immunological and behavioral systems (Plotsky, Bradley & Anand, 2000). The HPA axis conveys impulses such as pain, touch or pressure to neurons in the hypothalamus. These neurons produce peptides that travel to the anterior pituitary gland where corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) encourage the release of stored adrenocorticotrophic hormone (ACTH) into the systemic circulation. ACTH stimulates the synthesis and secretion of glucocorticoids from the adrenal cortex to mobilize energy substrates during stress in synergy with catecholamines released from the adrenal medulla. The resultant effect is stress-induced hyperglycemia, mobilization of fat and protein, insulin resistance, increased heart rate and blood pressure. Although these HPA effects may be protective at times, prolonged elevation of glucocorticoids has detrimental consequences.

The HPA axis is less sensitive in neonates. Although the hypothalamic and pituitary components are well established in early fetal life, the adrenal cortex is not. Therefore, although the neonate may be responsive to pain, the immature HPA is less able to mobilize glucocorticoids to maintain endocrine, immunological and behavioral stability (Plotskey et al.,

2000). Plotskey et al. (2000) suggest that the resultant catabolic state might become magnified in the absence of negative feedback of CRF and ACTH that would contribute to long-term sequelae when the neonate is subjected to repeated pain.

Analgesics administered intra-operatively to term infants have decreased physiological disturbances (increased heart rate, BP and intracranial pressure) and improved overall clinical outcomes including decreased incidence of sepsis, metabolic acidosis, hyperglycemia and disseminated intravascular clotting (Anand & Hickey, 1987; Anand et al., 1989; Anand & Aynsley-Green, 1985). In preterm infants undergoing thoracotomies (Anand et al., 1992) or mechanical ventilation (Kelly, & Finer, 1984; Raju, Vidyasagar, Torres, Grundy & Bennett, 1980), analgesia reduced heart rate and blood pressure. Preterm infants who did not receive analgesia for these noxious stimuli had significantly more physiological responses and were more likely to develop intracranial hemorrhages, pneumothoraces or other complications than infants who received analgesia (Anand et al., 1992).

Significant hormonal and metabolic responses have been measured in fetuses (Giannakouloupoulos et al., 1994; Teixeira et al., 1996), and in preterm (Anand & Aynsley-Green, 1985; Stevens & Johnston, 1994) and term (Anand, 1995; Anand et al., 1992; Kehlet, Brandt & Rem, 1980; Porter, Wolf & Miller, 1998) neonates undergoing minor procedures and surgical operations. During painful procedures, these responses stimulate the release of “stress hormones” (e.g. catecholamines, corticosteroids, growth hormones, glucagons, epinephrine and norepinephrine) that increase heart rate and blood pressure, enhance liver and muscle glycogen breakdown, stimulate metabolic rate and improve mental activity (Anand & Hickey, 1987; Anand et al., 1992; Guinsberg et al., 1998). In term infants undergoing cardiac surgery, anesthesia blunted stress responses and facilitated wound healing (Anand & Hickey, 1987).

Behavioral Responses

Facial expression, cry and body movement are the most widely documented behavioral responses to pain in infants. Irrespective of gestational age or maturation, brow bulge, eye

squeeze and nasolabial furrow are consistent facial expressions following painful stimulation (Grunau, Johnston & Craig, 1990; Grunau & Craig, 1987; Stevens & Johnston, 1994). Facial activity is considered the gold standard of behavioral responses for pain in neonates (Craig, 1998).

Cry has been used as an indicator of pain (Johnston & O'Shaughnessy, 1988; Michellson, Sirvio & Wasz-Hockert, 1977; Michelsson, 1971; Michelsson, Jarvenpaa & Rinne, 1983; Michelsson, Raes, Thoden & Wasz-Hockert, 1982; Porter, Miller & Marshall, 1986; Porter, Porges & Marshall, 1988). Cry can provide information about the neonate's biological integrity (Lester, 1984; Lester & Zeskind, 1979). Cry characteristics have been examined by their presence or absence (Owens & Todt, 1984), latency (Franck, 1986), percentage of occurrence and duration (Franck, 1986) and acoustic parameters (Fuller, 1991; Fuller, Connor & Horii, 1990; Fuller & Horii, 1988; Stevens, Johnston & Horton, 1994). However, preterm or acutely ill neonates are often unable or too immature to produce a robust cry, or they may be unable to produce a cry because of the presence of an endotracheal tube through the glottis. Therefore, the presence of cry is not a reliable indicator for neonate pain, especially in preterm neonates.

Body movements have also been used as pain indicators (Craig, Whitfield, Grunau, Linton & Hadjistavropoulos, 1993; Franck, 1986; Walden, 1997). However, the quality of movement is dependent on gestational age and therefore may not be a reliable indicator for neonate pain. Preterm or acutely ill infants may lack sufficient energy to demonstrate body movements in response to pain. Their movements are less organized and less observable than healthy term infants (Craig et al., 1993; Grunau, Holsti, Whitfield & Ling, 2000; Johnston & Stevens, 1996). In an observational study of pain responses of preterm neonates less than 1000g, Grunau et al. (2000) found that body activity such as postural, trunk and limb

movements were associated with painful procedures whereas tremors, startles and twitches were not related. Differences in the response to painful procedures were, however, subtle and often missed by observers.

Craig et al. (1993) examined behavioral responses of preterm and term neonates experiencing painful and non-painful procedures. A heel lance procedure was used to examine responses during four phases including baseline, swabbing, lance and recovery. Physiological data, facial activity and bodily activity were collected. In all gestational age groups, responses were greatest during the lancing phase. Although neonates as young as 25 weeks gestation demonstrated facial activity in response to heel lancing, there was less facial activity compared to the older neonates. Physiological responsivity varied with the phases of the heel lance procedure but did not vary with gestational age.

Johnston, Stevens, Craig and Grunau (1993) compared behavioral pain responses of four groups (preterm, term, 2 months old and 4 months old) of infants during a painful procedure. Although the pattern of facial activity increased during the painful procedure across all age groups, there was less facial activity in the preterm group than the term and older infants. Stevens (1993) examined preterm infants' ($n = 124$) physiological and behavioral responses to heel lances. Facial actions including brow bulge, eye squeeze and nasolabial furrow were increased during the lance and squeeze phases of the heel lance procedure but gestational age had no effect on facial activity. These findings may have been related to the narrow range of gestational age group examined (32 – 34 weeks gestation).

In contrast to gross motor movements, the flexor withdrawal reflex is a measure of nociceptive function in the CNS that parallels perceived pain in adults. The flexor reflex threshold can be assessed by applying various sizes of von Frey filaments or hairs to the sole of the foot and recording the force required to elicit the pain response (Fitzgerald, 2000). Animal

data (Ekholm, 1967; Fitzgerald & Gibson, 1984; Andrews & Fitzgerald, 1994) suggest that the thresholds for these reflexes are lower in newborns compared to adults, such that eliciting a flexor reflex does not always require a painful stimulus. Development of the flexor withdrawal reflex occurs with post-conceptual age (PCA), with responses becoming more discrete and measurable as PCA increases. Preterm neonates less than 30 weeks gestation have lower thresholds for the flexor withdrawal response and their reflexes are exaggerated compared to adults (Anand, 1993; Fitzgerald, 1993b; Fitzgerald, 2000). Fitzgerald, Shaw and MacIntosh, (1988) compared the development of the cutaneous flexor reflex in preterm infants born at 25 to 34 weeks gestation and tested at 27 to 39 weeks PCA, to full term healthy neonates. The thresholds were lower in the neonates less than 29 weeks PCA compared to term neonates. Although the flexor withdrawal reflex in infants does not have all the same properties compared to adults, it can be used as a measure of sensitivity for painful stimuli.

Pain can affect and be affected by the neonate's behavioral state. Behavioral states are discrete behaviors that represent arousal level. State changes have been used to describe a shift along a continuum of arousal from sleep to wakefulness (Pratt, 1937, Sokolov, 1963). Neonates spend much greater proportions of time in sleep versus awake states compared to older infants and the proportion of time spent in sleep states is related to gestational age, with preterm neonates spending the greatest amount of time in sleep (Booth, McGrath, Brigham, Frewen & Whittall, 1989; Parmelee & Stern, 1972; Stevens, 1993; Watt & Strongman, 1985). By 32 weeks gestation, individual differences in state patterns are detectable (Holditch-Davis, 1990). Although behavioral state is less identifiable in preterm neonates, several studies (Gabriel, Grote & Jonas, 1981; High & Gorski, 1985; Holditch-Davis, 1990) have reported that preterm neonates have sleep and wake states that may affect their responsiveness to their environment. Grunau and Craig (1990) examined the effect of infant state on behavioral responses to painful

stimuli. Latency to cry was greatest and facial actions including brow bulge, eye squeeze, nasolabial furrow and open mouth were decreased in the neonates who were in sleep states prior to the painful procedure. Similarly, Stevens (1993) found that in response to heel lancing, infants in a quiet sleep state prior to the painful procedure had smaller changes in facial actions compared to those in active sleep. Infants in the active awake state had greater proportions of all facial actions.

In summary, neonates' cardiovascular, hormonal and metabolic responses are highly variable and non-specific to pain. Physiological changes result from activation of sympathetic and parasympathetic nervous systems, and responses to noxious stimuli are limited to the immediate post noxious period. As such, physiological responses are inconsistent and unsustainable over time. Alternatively, behavioral responses have been found to be significantly greater in pain situations than non-pain or stressful situations and may be more specific in defining pain (Guinsburg et al., 1998; McCarthy, McCue & Walker, 1997). Therefore, combining physiological and behavioral responses may provide a more comprehensive assessment of pain, and further differentiate between pain and stress. Pain assessment in neonates is now generally undertaken using composite measures. However, as the focus of this thesis is on pain management, the body of available pain assessment measures will not be discussed in detail here. The physiological and behavioral responses to painful stimuli are summarized in Appendix A.

Long-term Consequences of Pain.

There is some evidence to suggest that early pain responses influence later pain behaviors, although the results of these studies are somewhat inconsistent. Most of the data are derived from animal models that suggest that repeated painful stimuli result in permanent structural and functional reorganization of the nervous system and alteration in future pain

responses (Fitzgerald & Anand, 1993; Plotsky et al., 2000; Ruda, Ling, Hohmann, Peng & Tachibana, 2000). Reynolds, Alvares, Middleton and Fitzgerald (1997) reported that skin wounds inflicted on rat pups caused hyper-innervation and decreased pain thresholds in the injured area that lasted three months after the painful event. Rats subjected to recurrent pain from day one of life developed changes in the receptive field of their dorsal horn neurons that persisted over time. In addition to the physiological/structural changes associated with repetitive pain, Anand et al. (1999) found that behaviors were also altered over time. Newborn rat pups that received repetitive painful stimuli four times a day for 7 days had decreased pain thresholds as compared to rat pups that did not receive repeated pain (control). Furthermore, the adult rats that had received repeated pain stimuli demonstrated more stress-related behaviors such as freezing or digging than the control rats. Ruda et al. (2000) found that rat pups that received repeated painful stimuli (injections into the left hind paw) had changes in their spinal nociceptive neuronal circuits compared to control rats. There was a loss of neurons and a decrease in nociceptive primary afferents in rat pups that had experienced repeated pain. As adults, these rats also exhibited increased responses to noxious and non-noxious stimuli relative to the control rats.

In human neonates, the capacity to respond to pain is present in early fetal life (Fitzgerald, 1993a, 2000). However, the capacity of the descending inhibitory mechanisms to modulate pain are less developed. Thus, preterm neonates may be responsive to pain but lack inhibitory mechanisms to modulate its intensity. The resultant lack of inhibition may contribute to long-term sequelae when the preterm neonate is exposed to repeated painful stimuli. Fitzgerald et al. (1988, 1989) found that the threshold for flexor withdrawal reflex in preterm neonates was reduced with repeated heel lances. Compared to the intact contralateral heel, the injured heel had a lower withdrawal reflex. Similarly, Andrews and Fitzgerald (1999) compared

the flexor withdrawal threshold in infants with ischemic leg injuries. The contralateral healthy leg had higher withdrawal thresholds.

Johnston and Stevens (1996) compared pain responses of neonates who were born at 28 weeks of gestation and were hospitalized in a NICU for 4 weeks (32 weeks post conceptional age) to neonates who were born at 32 weeks of gestation. Heart rate, oxygen saturation and three facial actions (brow bulge, nasolabial furrow and eye squeeze) were used as individual pain indicators. Neonates were observed during a routine heel lance. Neonates who had spent 4 weeks in the NICU had significantly higher heart rates ($F = 25.13$, $p < 0.001$) and significantly lower oxygen saturation ($F = 20.14$, $p < 0.001$) than neonates born at 32 weeks. In contrast, the neonates who had spent 4 weeks in the NICU had significantly less eye squeeze ($F = 9.85$, $p < 0.002$) and a trend towards less nasolabial furrow ($F = 3.32$, $p < 0.076$) than neonates who were born at 32 weeks. A stepwise regression analysis with Apgar score, weight at birth and at data collection, severity of illness at the time of data collection, PCA and total number of invasive procedures revealed that the number of painful procedures that the neonate had experienced prior to the painful procedure being evaluated explained most of the variance in facial expressions. Factors that influenced the variance in physiological responses were Apgar scores and birth weight.

Grunau, Whitfield and Petrie (1994a) examined (a) whether parents who had preterm neonates hospitalized in an NICU reported higher levels of pain perception in their toddlers, and (b) whether parental pain ratings were related to child temperament or parenting styles. Neonates were stratified into 4 groups based on birth weight: (a) < 801 grams, (b) 801 - 1000 grams, (c) 1500 - 2499 grams and (d) > 2499 grams. Measures of cognitive development, neonatal temperament and pain sensitivity were obtained from the mothers at 18 months of age. Statistically significant differences in pain perception were reported by parents across the

groups. The two lower weight groups were rated by parents as significantly less sensitive to pain compared with the larger neonates ($F = 4.43$, $p < 0.005$). Pain sensitivity was unrelated to child temperament in the weight group < 801 grams but significantly related for all other groups. Parenting style and home environment were not associated with reported pain sensitivity. Preterm neonates hospitalized in NICU's and exposed to numerous painful stimuli were reported by mothers as less sensitive to pain.

Grunau, Whitfield, Petrie and Fryer (1994b) later matched 18 preterm neonates (birthweight < 1000 grams) with full term neonates to examine the relationship between repeated painful stimuli during prolonged hospitalization and increased somatic complaints that could not be explained medically, such as unexplained headaches or leg pains. Psychological assessments and IQ tests, adjusted for corrected age (CA), were done at 3 and 4 1/2 years of age. Mothers rated the frequency of their child's somatic complaints. Twenty five percent of preterm neonates had somatic scores, evaluated by their mothers, above a level considered clinically significant by the researchers. None of the term neonates' scores reached clinically significant levels. Personality traits of the children were not related to somatic complaints. Children who when neonates had longer stays in the NICU had increased somatic complaints. Although the outcome measures were not blinded or validated, the health status of the preterm neonates were not controlled for and the data were obtained from mothers, the findings suggest that prior pain may contribute to somatization.

Taddio, Goldbach, Ipp, Stevens and Koren (1995) examined the effectiveness of Eutectic Mixture of Local Anesthetics (EMLA) for relieving procedural pain associated with immunization. Males circumcised within 2 days of birth had significantly longer crying bouts (53 vs. 19 seconds, $p = 0.02$) and higher pain intensity scores as measured on the Visual Analogue Scale (VAS) (8 vs. 6, $p = 0.01$) at immunization at two months of age than males who

were not circumcised. However, the results were not derived from a RCT but post hoc analyses of previous data (Taddio, Nulman, Goldbach, Ipp & Koren, 1994). In addition, the results were based on a small sample size ($n = 42$) and visual analogue scale reports by health professionals who were not blinded to group allocation. There was no actual assessment of the neonate's pain response, based on physiologic or behavioral indicators. Taddio et al. (1997) later reported that male neonates who received EMLA prior to circumcision had 12 to 24 % less facial activity ($p < 0.001$) and had 10 beats/min less increase in heart rate ($p < 0.007$) than male neonates who did not receive EMLA. This study had an adequate sample size ($n = 68$) and was a double blinded randomized controlled trial.

In a cross-sectional and longitudinal study with neonates of different gestational ages and postnatal ages ($n = 152$), Porter et al. (1999) found that preterm and term neonates showed increased magnitude of physiologic and behavioral responses to increasingly invasive procedures. Irrespective of age, neonates became more agitated in response to more painful procedures. There was no significant interaction between gestational age and PCA with pain responses in the first week of life. However, when preterm neonates were observed after they reached 36 weeks PCA, the magnitude of their physiological responses differed from neonates born at term. Neonates born closer to term displayed smaller heart rate increases to procedures compared with all other gestational age groups. The most variability occurred with neonates less than 28 weeks of gestation who were 36 weeks PCA. Similar to Johnson and Stevens (1996), heart rate response increased with postnatal age. Porter et al. (1999) did not find behavioral differences between preterm and term neonates.

In contrast to studies suggesting that physiological and behavioral pain responses change as a result of postnatal age, Oberlander, Grunau, Whitfield, Fitzgerald, Pitfield and Saul (2000) found that former preterm neonates ($n = 24$) did not respond differently to painful procedures

when compared to a cohort of term neonates ($n = 24$). Preterm neonates were observed during a finger lance procedure at 4 months corrected age. Term, healthy neonates were observed at 4 months of age. The groups were not matched in any way. Facial actions and heart rate reactivity were used as indicators of pain. The finger lance was divided into phases: baseline, lance, recovery. There were no differences in facial pain scores between preterm and term neonates during the three phases ($F = 0.10$, $p = 0.91$). However, during the recovery phase, 43% of the preterm neonates compared to 12% of term neonates showed no facial activity, suggesting a more rapid return to baseline after the lance procedure for the preterm group. No differences in heart rate reactivity with this small sample size were found between groups ($F = 2.50$, $p = 0.08$). These results suggest that pain responses to an acute event are similar between former preterm and term neonates. However, it is not clear whether the differences represent developmental differences between preterm and term neonates, or cumulative effects of early pain exposure.

To understand the long-term effects of repeated pain, Grunau, Whitfield and Petrie, (1998) followed the ELBW infants from previous studies (Grunau et al., 1994a, 1994b) for 10 years. The children were asked to observe 24 pictures of children in pain from medical, recreational and activities of daily living settings. Fear and embarrassment were also depicted in the photographs. Somatization and social competence were measured by parent questionnaires. For the ELBW group, medical related pain was rated significantly higher than fear and embarrassment. Pain intensity was not correlated with length of hospitalization. No other differences between the groups were found. These data suggest that early pain may affect long-term pain responses as perceived by parents.

In summary, very little empirical data concerning long-term consequences of pain in human neonates exist. Animal data suggest that prolonged exposure to pain alters biobehavioral responses and results in permanent shifts in autonomic arousal states. However, human studies

have yielded conflicting results. Due to inconsistent findings and lack of methodologic rigor in some of the earlier studies, long-term differences in pain responses between former preterm neonates and term neonates require further study.

Pain Management

Although pain management for neonates has improved over the past decade for some situations (e.g. post-operative pain), pain management for procedural pain remains minimal or nonexistent (Anand & Selanikio, 1996; Barr, 1992; Boreus, 1990; Craig & Grunau, 1993; Franck, 1991; Johnston, Stremler, Horton, & Friedman, 1999; VanKeuren & Eland, 1997). Attitudes and beliefs concerning pain management are influenced by (a) inadequate physician and nursing education regarding the safety and efficacy of analgesic agents (Ferrell, Grant, Ritchey, Ropehan & Rivera, 1993), (b) concern for addiction and risks to the neonate (Anand & Hickey, 1987; McLaughlin et al., 1993) and (c) inability to adequately assess pain in neonates (Anand, 1993; Anand & McGrath, 1993; Barr, 1992; McIntosh, VanVeen & Brameyer, 1993).

Sucrose

The administration of sucrose has been the most frequently studied non-pharmacological intervention for the relief of procedural pain in newborn neonates. Sucrose has promoted calming behaviors and reduced acute procedural pain in preterm and term neonates (Blass & Hoffmeyer, 1991). Sucrose has been thought to reduce crying time, or distress vocalization, by eliciting licking, swallowing and hand-mouth behaviors that prevent crying. Blass and Hoffmeyer (1991) demonstrated that sucrose is not detected in the mouth until 20 - 40 seconds after its delivery, and that only trace amounts of sucrose can be detected chemically in the saliva. Neonates who receive small amounts of sucrose remain in awake and alert states, and place their hands in their mouths. Hand-mouth behaviors only appear after crying stops, therefore disputing the argument that crying only stops because it is incompatible with hand-

mouth or sucking behaviors. These results imply that the efficacy of sucrose as a pain relieving intervention is more complex than simply preventing the licking, swallowing and mouthing behaviors that preclude crying.

Sucrose is a disaccharide consisting of fructose and glucose. Sucrose was first introduced to the West by the soldiers of Alexander the Great, who entered India in 325 B.C. (Neu & Koldovsky, 1996). In later centuries, the use of sucrose as a sweetening agent was spread by the Arabs and the Crusaders, and was introduced into the New World by Columbus in 1493. Today sucrose is used as a common household sweetening agent. Compared to sucrose; fructose, glucose, maltose and lactose are 1.7, 0.75, 0.33 and 0.6 times as sweet as sucrose, respectively (Martindale, 1989). The soothing and calming properties of sucrose have been anecdotally described by generations of parents and grandparents who claim that sweet solutions calm distressed neonates. Current medicinal uses include sucrose in suspensions for oral medications, possibly to conceal the bitter taste of the active pharmacological ingredients. The calming effects of sucrose are thought to be related to endogenous opioid mediation and non-opioid systems (Blass & Hoffmeyer, 1991). However, the mechanisms underlying the efficacy of sucrose remain speculative. Indirect evidence for endogenous opioid mediation has been derived primarily through studies with animal models.

Mechanisms of sucrose. Although several different hypotheses regarding the underlying mechanisms of sucrose exist, there is one that is the most plausible and has the most support. The *sweet taste* of sucrose is proposed to promote analgesia through activation of endogenous opioids that attenuate nociceptive information at the level of the dorsal horn (Ganong, 1995). Similarities between oral sucrose and morphine injections have been demonstrated in newborn rats (Blass & Fitzgerald, 1988; Blass & Shide, 1994; Kehow & Blass, 1986) and chicks (Panksepp, Siviy & Normansell, 1986). Rat pups had diminished distress vocalizations

following an electrical charge to their hind paw after the administration of intraoral sucrose (Kehoe & Blass, 1986). Unlike sucrose, water did not affect latency or distress vocalizations. Similar reductions in vocalization were reproduced by exogenous morphine administration. These reductions in distress vocalizations were reversed with the administration of naltrexone (an opioid antagonist) that suggests an opioid mediation. The results of animal studies suggest that sucrose is (a) anti-nociceptive, (b) effective with a short latency, and (c) effective after the painful stimulus has ceased.

Further studies examining taste as the mechanism for sucrose have shown that rat pups preferentially ingest sucrose over milk and other non-sweet solutions during painful and stressful events (Blass & Fitzgerald, 1988). Rat fetuses that received intrauterine injections of apple juice prior to delivery preferentially ingested apple juice over milk 15 days after birth. Compared to control rats, rats that received intrauterine apple juice consumed greater amounts of apple juice after birth (Strickrod, Kimble & Smotherman, 1982). Chronic exposure to sweet tastes appears to alter subsequent responses to thermal pain. These altered responses may be explained by the high levels of endogenous opioids associated with exposure to sweet tastes. Rats receiving intraoral saccharine for 28 consecutive days did not respond to morphine injections for painful thermal stimuli. Unlike the control rats that did not receive saccharine, the experimental rats appeared to develop a tolerance to morphine (Lieblich, Cohen & Ganchrow, 1983). Furthermore, the rats that received saccharine did not respond to the opioid antagonist naltrexone (Lieblich et al., 1983). Therefore, although the efficacy of sweet tastes appears to provide opioid-mediated analgesia in the rat model, repeated doses of sweet tastes may result in tolerance to subsequent opioid administration.

Due to ethical reasons, much of what has been studied in animal models cannot be replicated with human neonates. Therefore, although the efficacy of sucrose is reduced in

animal models in the presence of high levels of endogenous opioids, the relationship in human neonate remains theoretical. Smith, Stevens, Torgerson and Kim, (1992) compared pain responses of post term infants to healthy full term infants. Term infants were significantly more calmed by sucrose, as measured by cry duration, than post term infants ($F = 8.66$, $p. < 0.01$). The authors hypothesized that the release of *B* endorphins associated with post-term infants, resulted in tolerance to sucrose. Similar to animal models, high levels of endogenous opioids appear to alter responsiveness to morphine (Lieblich et al., 1983). Blass and Ciaramitero, (1994) examined human neonates, born to mothers who were maintained on methadone during their pregnancy to draw comparisons between endogenous opioids and responsiveness to sucrose. Neonates of mothers exposed to methadone were not calmed by sucrose. Furthermore, sucrose did not prevent these neonates from becoming agitated when a pacifier to promote NNS was removed from their mouth. Although the sucrose was taken avidly, the neonates only stopped crying when a pacifier was returned to their mouth or the neonate placed his/her hand into the mouth. Sucrose administration did not reduce heart rate. Similar to animal models, chronically high methadone levels, appear to alter responsiveness to sucrose. Conversely, NNS may have soothed neonates whose mothers were on long-term methadone because the non-opioid pathways were intact.

Taste receptors that detect sweetness are found at the anterior tip of the tongue where sucrose is administered. Taste receptors are present in human neonates by the end of the eighth week of gestation and sensory nerve fibers from the receptors of the tongue to the brainstem are established by 26 - 28 weeks of gestation (Moore, 1988). Taste fibers unite in the medulla oblongata, where they synapse with fibers for touch, pain and temperature (Moore, 1988). Impulses are then relayed to the cerebral cortex for interpretation. In both preterm and term and older neonates, sweet tastes are preferred over fats, proteins, lactose and water (Blass &

Ciaramitero, 1994; Graillon, Barr, Young, Wright & Hendricks, 1997). Sucrose preference, as measured by intake, was related to sweetness in all age groups (Blass & Ciaramitero, 1994). Rank ordering of sugars by adults and neonates were shown to be identical, with sucrose preferred to fructose, which is preferred to glucose, which is preferred to lactose (Blass & Smith, 1992). Similar to animal models, adult, term and older neonates preferentially ingest sweets or fats over non-sweets during stressful situations and this relationship is probably opioid mediated. Behavioral responses to non-sweet tastes are similar across age groups and include raised cheeks and narrowed or tightly closed eyes, wrinkled nose and eye brows pulled together (Rosenstein & Oster, 1988). Responses to sweet tastes include facial relaxation, hand-mouth behaviors and sucking behaviors.

Taste-induced analgesia in animal and human newborns is rapid, enduring and dependent on the ability to detect sweet taste. Sucrose has been administered to preterm, term and older neonates by syringes (Abad, Diaz, Domenech, Robayna & Rico, 1996; Johnston et al., 1999; Johnston, Stremler, Stevens, & Horton, 1997; Ramenghi, Griffith, Wood & Levene, 1996a) droppers (Rushforth & Levene, 1993), cups (Blass & Shah, 1995; Ramenghi, Evans & Levene, 1999) or dipped on pacifiers (Graillon et al., 1997; Ramenghi et al., 1999; Stevens et al., 1999). One study (Ramenghi et al., 1999) compared the efficacy of sucrose using different routes of sucrose administration in preterm neonates. In a cross over design, neonates received sterile water or sucrose prior to a heel lance. The solution was given through a nasogastric tube that passed directly in the stomach. For the second intervention, the neonate received the same solution via a syringe onto the tongue. Pain responses were measured by a behavioral pain score (0 – 15) comprised of facial expressions (brow bulge, eye squeeze, nasolabial furrow and open mouth). Compared to sterile water, sucrose administered directly on the tongue significantly reduced crying time (6 vs. 22 seconds, $p = 0.006$) and behavioral pain scores (5 vs. 9, $p =$

0.002). Neither sucrose nor sterile water delivered directly into the stomach reduced procedural pain. Sucrose is hydrolyzed into glucose and fructose through the intestinal epithelium that is present by 26 weeks gestation (Aldoretta & Hay, 1995; Naqui, Diskinis & Khattack, 1999; Neu & Koldovsky, 1996; Schanler, 1995). Given the rapid effects of intraoral sucrose, it is unlikely that hydrolysis in the small intestine is responsible for its pain relieving properties. Taste appears to mediate the opioid response.

Evidence of efficacy of sucrose. Two systematic reviews (Stevens et al., 1997; Stevens & Ohlsson, 1998) have addressed the efficacy of sucrose for procedural pain in neonates. In the first review, Stevens et al. (1997) obtained data from published randomized controlled trials (RCTs) where term and preterm neonates received sucrose for a heel lance or venepuncture. Data were combined across studies using a random effects model producing a point estimate and 95% confidence interval (Stevens et al., 1997). Studies were included in the review if: (a) the design was a blinded RCT, (b) the treatment intervention included sucrose administration, (c) the pain stimulus was a common medical NICU procedure, (d) the outcomes were behavioral, physiological, hormonal or metabolic and (e) the study population was neonates. Thirteen RCTs were identified but only one study with preterm neonates ($n = 16$) and four studies with term neonates ($n = 255$) met the inclusion criteria for a meta analysis. The preterm neonates included in the study were born between 29 - 36 weeks of gestation and were relatively stable. Studies were excluded from the meta analysis if the painful stimulus was not defined or measured, the data were not extractable, the pain outcomes varied or the method of sucrose administration varied from syringe, dropper or pacifier. Other limitations in the ability to synthesize data included lack of consistent painful stimuli.

The primary outcome was the proportion of crying time 3 minutes after the painful stimulus. The proportion of crying time was highest in the groups of neonates who received

0.18g of sucrose (77.3%) or water (63.3%). The proportion of time spent crying for all other sucrose dose groups (0.24g, 0.48g, 0.50g and 1.0g) was significantly lower than the groups who received 0.18g sucrose and water. Sucrose concentrations greater than 0.24g (2 ml of 12% sucrose solution) given by syringe or pacifier approximately 2 minutes prior to a painful stimulus was the most effective in diminishing proportion of cry. There was no significant clinical benefit to administering doses greater than 0.50grams (2 ml of 24% sucrose solution). No adverse effects have been reported when administering 24% sucrose via a pacifier. There were no differences in the proportion of crying time between preterm and term neonates. However, preterm neonates were greatly underrepresented in the meta analysis.

In the second review, Stevens and Ohlsson (1998) identified 15 studies that examined the safety and efficacy of sucrose for relieving procedural pain in neonates. The quality of studies was assessed according the methods of the Neonatal Collaborative Review Group that included: blinding of randomization, blinding of intervention, completeness of follow up and blinding of outcome measurement. Five of the studies were excluded because randomization to treatment vs. placebo group was not reported, one study was not a RCT and one study did not use a painful stimulus. Ten studies were included in the systematic review; four of the studies were previously reported in the first review (Abad et al., 1993; Abad et al., 1996; Gormally, Barr, Young, Alhawaf & Wersheim, 1996; Haouari, Wood, Griffiths & Levene, 1995), two studies used much smaller doses of sucrose (Johnston et al., 1999; Stevens et al., 1999), two studies included preterm neonates (Bucher et al., 1995; Ramenghi et al., 1996a), one study included term neonates (Rushforth & Levene, 1993) and one study compared sucrose and non-sucrose sweet tastes (Ramenghi, Wood, Griffiths & Levene, 1996b). No two studies measured the same physiological and/or behavioral outcomes following a variety of painful procedures (e.g. heel lances, venipuncture, intramuscular injections). Therefore, a meta-analysis could not

be performed. The systematic review could not identify the optimal dose of sucrose to reduce procedural pain. In addition, the systematic review could not provide data on the safety and efficacy of sucrose for very low birth weight, unstable and/or ventilated neonates. A summary of studies included in the two systematic reviews is included in Table 2.

Table 2

Summary of Sucrose Trials in the Systematic Reviews

Stevens et al. (1997)				
Study	Methods	Interventions	Results	Limitations
Abad et al. (1993) (abstract quality)	RCT, db, pc n=172 term 2 – 6 days old	2 ml (a) 12% sucrose, (b) 24% sucrose, (c) 12% dextrose or (d) water 2 min prior to heel lance	Significant reduction in mean % cry at 3 min in 12% and 24% sucrose groups. ANOVA showed significant group effect ($F = 4.04$, $p = 0.008$)	Little detail about heel lance procedure, no detail of randomization
Abad et al. (1996)	RCT, db n=16 (29-36 weeks gestation) 1 – 26 days old	2 ml (a) 12% sucrose, (b) 24% sucrose or (c) sterile water prior to venipuncture	Significant reduction in 24% sucrose. Univariate analysis of variance showed significant group effect ($F=4.26$, $p=0.02$)	Small sample, healthy preterm neonates. No detail of blinding of randomization
Blass et al. (1991)	RCT, db, pc n=30 term	2ml sucrose or water 2 min prior to heel lance	42% cry vs. 80% cry in sucrose vs. water	Small sample, no detail of blinding of randomization
Gormally et al. (1996)	RCT, db n=64 term	250ul of (a) 24% sucrose, (b) water x 3 doses at 30 second intervals (c) sucrose & carrying and (d) carrying 3 minutes prior to heel lance	Significant reduction in % cry for second & third minutes in sucrose & carrying. Repeated measures ANOVA showed an overall main effect ($F=2.7$, $p=0.05$)	Healthy term neonates. Lack of blinding
Haouari et al. (1995)	RCT, db n=60 term	2 ml of (a) 12.5% sucrose, (b) 25% sucrose, (c) 50% sucrose or (d) water 2 minutes prior to heel lance	Significant decrease in total crying time and duration of first cry in 50% sucrose. Significant decrease in heart rate in 50% group after 1 and 2 minutes.	No detail of blinding of randomization

Table 2

Summary of Sucrose Trials in the Systematic Reviews (continued)

Stevens & Ohlsson (1998)				
Study	Methods	Interventions	Results	Limitations
Abad et al. (1993) (abstract quality)	RCT, db, pc n=172 term 2 – 6 days old	2 mls (a) 12% sucrose, (b) 24% sucrose, (c) 12% dextrose or (d) water 2 min prior to heel lance	Significant reduction in mean % cry at 3 min in the 12% and 24% sucrose groups. ANOVA showed significant group effect. (F=4.04; p=0.008)	Little detail about heel lance procedure, no detail of randomization
Abad et al. (1996)	RCT, db n=16 (29-36 weeks gestation) 1 – 26 days old	2 mls (a) 12% sucrose, (b) 24% sucrose or (c) sterile water prior to venipuncture	Significant reduction in 24% sucrose. Univariate analysis of variance showed sig group effect (F=4.26, p= 0.02)	Small sample, healthy preterm neonates. No details of blinding of randomization
Bucher et al. (1995)	Crossover n=16 (27-34 weeks gestation)	2 mls distilled water or 50% sucrose prior to heel lance	Significant increase in heart rate with distilled water (p < 0.005) and decrease in crying in 50% sucrose (p < 0.002)	No detail on time interval between crossover. Small sample. Findings limited to healthy older preterm neonates
Gormally et al. (1996)	RCT, db n=64 term	250ul of (a) 24% sucrose, (b) water x 3 doses at 30 second intervals (c) sucrose & carrying and (d) carrying 3 minutes prior to heel lance	Significant reduction in % cry for second & third minutes in sucrose & carrying. Repeated measures ANOVA showed an overall main effect (F=2.7, p = 0.05)	Healthy term neonates. Lack of blinding

Table 2

Summary of Sucrose Trials in the Systematic Reviews (continued)

Stevens & Ohlsson (1998)				
Study	Methods	Interventions	Results	Limitations
Haouari et al. (1995)	RCT, db n = 60 term	2 mls of (a) 12.5% sucrose, (b) 25% sucrose, (c) 50% sucrose or (d) water 2 minutes prior to heel lance	Significant decrease in total crying time and duration of first cry in 50%. Significant decrease in sucrose heart rate in 50% group after 1 and 2 minutes.	No detail of blinding of randomization
Johnston et al. (1997)	RCT n = 85 (25-34 weeks gestation)	0.05mls (a) 24% sucrose, (b) rocking (c) sucrose & rocking, (d) water & rocking prior to heel lance	Sucrose alone or with rocking significantly reduces facial expressions ($F = 4.56$, $p < 0.005$).	Blinding of 2 groups only. Small doses
Ramenghi et al. (1996a)	Crossover n = 15 (32-34 weeks gestation)	1ml 25% sucrose or water 2 min prior to heel lance	Significant reduction in % cry over 5 min ($p = 0.018$) and duration of first cry ($p = 0.004$) in sucrose group	No detail about length of time between treatment. Small sample size
Ramenghi et al., (1996b)	RCT n = 60 term	2 mls (a) 25% sucrose, (b) 50% sucrose, (c) commercial sweetener, or (d) sterile water 2 min prior to heel lance	Significant decrease in %cry and duration first cry	No safety data on commercial sweetener
Rushforth & Levene, 1993	RCT n = 52 term	2 mls 7.5% sucrose, (b) water prior to heel lance	No differences in time to cry cessation No differences in % cry	Small dose. No data on timing of sucrose administration.. No information on blinding

Table 2

Summary of Sucrose Trials in the Systematic Reviews (continued)

Stevens & Ohlsson (1998)				
Study	Methods	Interventions	Results	Limitations
Stevens et al., (1999)	RCT, crossover n=122 (27-31 weeks gestation)	(a) prone positioning, (b) pacifier dipped in sterile water, (c) pacifier dipped in 24% sucrose 2 min prior to a heel lance	Significant decrease in composite pain score (PIPP) between the pacifier & water groups and control ($F=8.12$, $p < 0.005$), and pacifier with sucrose ($F=2.88$, $p < 0.001$). A trend towards lower PIPP with sucrose compared to water	Blinding of only 2 groups

Note. RCT = randomized controlled trial, db = double blinded, pc = placebo control

Studies with term and preterm neonates not in the systematic reviews. Johnston,

Stremmler, Horton & Freidman (1999) examined the pain responses of 48 preterm neonates born less than 34 weeks gestation. Pain responses associated with heel lances were measured for five 30-second-blocks using the Premature Infant Pain Profile (PIPP) (Stevens, Johnston, Petryshen & Taddio, 1996). The PIPP is a validated, composite measure of pain that includes physiological, behavioral and contextual indicators (Appendix B). Neonates were randomized to receive 0.05 ml of (a) 3 doses of sterile water, (b) 1 dose of 24% sucrose (0.012 grams) followed by 2 doses of sterile water, or (c) 3 doses of 24% sucrose (0.04grams). Significant differences between groups were found ($F = 9.14$, $p < 0.001$), favoring the repeated doses of sucrose groups across all blocks of time. Although the mean PIPP scores were lower in the repeated doses of sucrose groups compared to the single dose of sucrose groups, they were only significant in the last block of time (PIPP scores of 8.25 vs. 6.25). No significant differences in PIPP scores between the single dose of sucrose and sterile water were found ($F = 3.46$, $p = 0.078$). The study used a small sample size, very small doses of sucrose and did not control for the use of pacifiers.

Mellah et al., (1999) evaluated the efficacy of sucrose for heel lances in preterm neonates ($n=33$) greater than 33 weeks gestation. In a cross over design, neonates from two NICUs received 0.2 ml of water or 70% sucrose in a random order prior to two scheduled heel lances. Behavioral indicators (face, tone, sleep state, consolability) were used as measures of pain. The behavioral pain scale (scores 0 – 10) was adapted from the Douleur Aigue de Nouveau-ne (DAN) (Carbajal, Chauvet, Coudere & Olivier-Martin, 1999). No differences in baseline demographics between the two NICUs or between intervention groups were found. Differences in pain scores were found between the NICUs. In neonates admitted to one NICU, irrespective of the treatment order, sucrose significantly reduced pain scores (1.24 vs. 2.24, $p <$

0.01). In neonates admitted to the second NICU, sucrose did not significantly reduce pain scores (0.25 vs. 0.70). In the second NICU, water was significantly better ($p < 0.0001$). The study did not validate the measure prior to study commencement, nor did it control for the variability between NICU sites. In addition, personnel in the first NICU were more consistent, thereby the technician effect may have been a factor in the results.

Ors et al. (1999) compared sucrose and breast milk as pain relieving interventions. Term neonates ($n=102$) requiring heel lances were randomly allocated to receive 2 ml of (a) 25% sucrose, (b) human milk or (c) sterile water 2 minutes prior to the heel lance. The solution was delivered by syringe and sucking on the syringe or pacifier was not encouraged. Pain responses were measured by cry duration and heart rate changes. Median crying times were 36, 52 and 62 seconds in the sucrose, placebo and human milk groups respectively ($p = 0.0009$). The percentage of change in heart rate (beat-per-minute) at 1, 2 and 3 minutes was also significantly less in the sucrose group compared to placebo and human milk ($p = 0.008$). Although the interventions were not blinded, and there was no information about blinding of assessment pain outcomes, the results suggest that sucrose is superior to human milk and sterile water in reducing pain.

In a RCT, Isik,Ozek, Bilgen and Cebeci (2000) compared the analgesic effect of 2 ml 30% sucrose, 10% glucose, 30% glucose and sterile water for heel lances for healthy term neonates ($n = 113$). Pain was assessed by mean crying time, recovery time, maximum heart rate and percent change in heart rate at 1, 2 and 3 minutes. Mean crying time was shortest in the 30% sucrose group (60 seconds) compared to the other 3 intervention groups (102, 95 and 105 seconds respectively) ($p = 0.02$). No differences in other outcomes were found. These data suggest that sucrose is more efficacious for reducing duration of cry associated with heel lances in term neonates than glucose or sterile water. No data for preterm neonates were provided.

Other sweet tasting solutions as pain relieving interventions. Skogsdal, Eriksson and

Schollin (1997) examined glucose as a pain relieving intervention. Preterm neonates greater than 30 weeks gestation ($n = 120$) were randomly allocated into 4 equal groups: (a) no treatment, (b) 1 ml of 10% glucose, (c) 1 ml of 30% glucose and (d) 1 ml of breast milk. The solutions were administered via syringe 30 seconds prior to a heel lance. Pain was measured by the duration of crying and changes in heart rate and oxygen saturation. The mean gestational age of all neonates was 35.5 weeks. Neonates given 1 ml of 30% glucose cried significantly less than neonates in the control group (90 vs. 270 seconds, $p < 0.01$) and had significantly less heart rate (beat-per-minute) increases following the heel lance (5.4 ± 10.00 , vs. 9.5 ± 16.90 , $p < 0.05$). No other significant differences in cry duration or heart rate were found. There were no differences in oxygen saturation. Limited data were provided for comparing the safety and efficacy of these sweet solutions for neonates.

Non-Nutritive Sucking (NNS)

NNS is the provision of a pacifier or non-lactating nipple into a neonate's mouth to promote sucking behaviors without the provision of breastmilk or formula to provide nutrition (Barr et al., 1994; Blass & Hoffmeyer, 1991; Blass, Fillion, Rochat, Hoffmeyer, & Metzger, 1989; Campos, 1994; DiPietro, Cusson, O'Brien, Caughy & Fox, 1994; Woodson, Drinkwin & Hamilton, 1985). Franck (1987) found that pacifiers were ranked by NICU nurses as the first choice of pain relieving interventions. Although NNS has been used for generations, it has only recently been rigorously examined as a pain relieving intervention.

Mechanisms of action of NNS. The calming effects of NNS have been observed in human and rat neonates, but the mechanisms underlying effectiveness remain unclear. NNS is thought to produce analgesia in human infants through stimulation of orotactile and mechanoreceptors when a pacifier or non-lactating nipple is introduced into the infant's mouth. Unlike

the mechanisms of sucrose, the orotactile induced analgesia associated with NNS does not appear to be mediated through opioid pathways; it is not affected by the administration of naltrexone and its efficacy is terminated once sucking has ceased.

In rat neonates, orotactile stimulation with a non-lactating anesthetized dam to promote NNS has been found to decrease distress vocalization associated with thermal pain. Rat pups at 10 days of age showed delayed withdrawal latencies from heat when NNS was provided (Blass, Shide, Zaw-Mon & Sorrentino, 1999). Relative to isolated rats, rats lying in contact with other rats doubled their heat withdrawal latencies. Rats provided with NNS increased their heat-escape latencies by four times while rats positioned in hyperextension and allowed to receive milk infusion did not withdraw from thermal pain at all. Unlike the heat escape latencies in the isolated or contact groups, the pain relief associated with NNS was not blocked by large doses of naltrexone or norbinaltorphimine. Suckling pups given morphine had increased heat-escape latencies by 15 minutes, and the effects were observed for 60 minutes. Contact or isolated rats did not achieve maximum latency for 45 minutes and the effects were not observed by 60 minutes. These notions suggest that the effects of NNS, although not opioid mediated, may potentiate the effects of opioid analgesics.

Serotonin production may be responsible for the calming and analgesic properties associated with NNS (Spear, Frambes, Goodwin & Moody, 1994; Wang, Bowersox, Pettus & Gao, 1999; Williams, Rosenblatt & Hall, 1979; Zangen, Nakash & Yadid, 1999). The involvement of serotonergic systems in the modulation of pain are well documented in the management of adult pain (Jung, Staiger & Sullivan, 1997; Max, 1994). Serotonin and serotonin reuptake inhibitors appear to facilitate the release of *B* endorphins that inhibit the transmission of nociceptive impulses. Previous data suggest that *B* endorphins play a role in analgesia in post term infants (Smith et al., 1992). Serotonin mediated analgesia, as measured

by *B* endorphin levels, is observed when serotonin and serotonin reuptake inhibitors are injected into the arcuate nucleus and nucleus accumbens of adult rats (Wang et al., 1999). Compared to control rats, rat pups that had had a surgical transection of their serotonergic system, had decreased *B* endorphins despite injections of serotonin or serotonin reuptake inhibitors. The ability to relieve pain appears to be related to the organism's neuronal ability to produce serotonin. In the rat model, intracerebroventricular boluses of serotonin reuptake inhibitors decreased pain responses associated with subcutaneous injections of formaldehyde, thermal pain and neuropathic pain created by tight ligation of spinal nerves. The pain inhibitory effects of serotonin and serotonin reuptake inhibitors were prevented by injection of serotonergic antagonists. However, the inhibitory effects were not prevented by the opioid antagonist naloxone. These results indicate that serotonin provides analgesia in rats through non-opioid mechanisms.

Jung et al., (1997) conducted a systematic review of 19 studies where the efficacy of serotonin reuptake inhibitors for the management of pain was examined. Although none of the studies included neonates or children, serotonin reuptake inhibitors consistently reduced chronic pain associated with headaches, diabetic neuropathy, post-herpetic neuralgia and fibromyalgia. No data on acute procedural pain exist but studies with animals have indicated that pain responses to mechanical stimuli are reduced with selective serotonin reuptake inhibitors.

There is some evidence that the serotonergic system promotes calming through attachment and suckling behaviors (Spear et al., 1994; Williams et al., 1979). In one animal study (Spear et al., 1994), serotonin reuptake inhibitors reduced the frequency of rat pups detaching and re-attaching to a non-lactating anesthetized dam. There was a trend for a dose related decrease in re-attaching behaviors with larger doses. Serotonin reuptake inhibitors also decreased the frequency of nipple switching and increased the time spent attached to the non-

lactating breast. Serotonin reuptake inhibitors did not increase suckling behaviors when weight gain was used as a proxy for suckling. Control rats had significantly more weight gain than rats that received serotonin. Weight gain may not be a valid indicator of suckling.

Similar results were found when serotonin receptor blockers, that prevent the neuronal reuptake of serotonin, were injected into rat pups (Williams et al., 1979). Serotonin receptor blockers increased the percentage of suckling in rat pups between 10 and 25 days. These agents also reinstated suckling behaviors in weaned pups. Rats younger than 10 days of age all suckled, regardless of whether they received serotonin or saline. Similar to the previous study (Spear et al., 1994), serotonin reuptake inhibitors did not increase suckling behaviors in rats older than 35 days. However, these older rats were more settled than the control group. The age related differences might reflect developmental maturation of the serotonin system whereby younger rats have immature serotonergic systems and older rats may have other mechanisms that contribute to the abandonment of suckling at weaning. These data support the hypothesis that serotonin modulates attachment behaviors to a nipple, similar to NNS, but does not appear to influence suckling, which is associated with ingestion. Further research to examine possible mechanisms for serotonin mediation, in the absence of feeding, is required.

In vitro brainstem-spinal cord preparations from newborn rats have been used to locate the area in the brain responsible for sucking reflexes (Jia, 1997). A rhythmical sucking-like activity of the hypoglossal nerve as the index of sucking was used and a fluorescent dye was injected into newborn rats on postnatal 0 to 3 days. The tongue's rhythmical activities persisted after removal of the dorsal medulla oblongata, the caudal pons and trigeminal spinal nucleus. The researchers concluded that the central rhythm generator for sucking is localized in the ventromedial medulla oblongata including gigantocellular reticular nucleus and ventroreticular.

Further research to clearly identify the area responsible for sucking is required in order to determine possible interventions to reduce or eliminate pain in neonates.

Evidence of efficacy of NNS. The provision of NNS has been studied as a method of relieving pain in term and preterm neonates. Pinelli and Symington, (1998) examined the efficacy of NNS in a systematic review for many neonatal outcomes. Nineteen studies met the inclusion criteria; 13 were RCTs and 6 utilized non-randomized designs (Bernbaum, Pereira, Watkins & Peckham, 1983; Burroughs, Anderson, Patel & Vidyasager, 1981; Burroughs, Asonye, Anderson-Shanklin & Vidyasager, 1978; DeCurtis, McIntosh, Ventura & Brooke, 1986; DiPietro et al., 1994; Ernst et al., 1989; Field et al., 1982; Gill, Behnke, Conlon, McNeely & Anderson 1988; Gill, Behnke, Conlon, McNeely & Anderson, 1992; Kanarek & Shulman, 1992; Mattes et al, 1996; McCain, 1992; McCain, 1992; Measel & Anderson, 1979; Pickler, Higgins & Crummette, 1992; Pickler, Frankel, Walsh & Thompson, 1996; Sehgal, Prakash, Gupta, Mohan & Anand, 1990, Szabo, Hillemeier & Oh, 1985; Widstrom et al, 1988). The primary outcome was length of stay. Preterm neonates who were provided with a pacifier during gavage feedings were discharged from hospital significantly earlier than preterm neonates who were not provided with NNS (7.1 days, CI -12.6, -1.7). The review did not reveal any other benefits of NNS but none of the studies followed neonates past discharge. Although NNS has historically been used by family members as well as health care professionals, very little rigorous research exists in relation to procedural pain relief.

Campos (1994) studied 60 healthy full term neonates in a RCT involving a routine heel lance. Neonates were randomized to receive routine nursing care ($n = 20$) or two types of comfort measures: rocking ($n = 20$) or NNS ($n = 20$). Neonates' cry, heart rate and behavioral state were recorded 30 seconds before the heel lance and every minute for eight minutes after the heel lance. The duration of crying was significantly longer in the control group ($F=6.43$, $p <$

0.01) than either of the comfort groups and the time to stop crying was significantly shorter in the group who received NNS ($F = 4.31$, $p < 0.05$). NNS also resulted in significantly more time spent in active sleep. No statistically significant differences were found in any group after eight minutes. The intervention was not blinded, and the sample size was small and therefore likely under powered. In addition, no information about the painful procedure was provided and therefore it is difficult to compare the results with those from other studies.

Combined Sucrose and NNS as Pain Relieving Interventions

The combination of sucrose and NNS reduces pain responses associated with heel lances (Blass & Ciaramitero, 1994), immunizations (Allen, White & Walburn, 1996; Schanler, 1995) and circumcisions (Blass & Hoffmeyer, 1991; Zahorodny, David, Estrada, Co & Marshall, 1999) in term neonates and immunizations in infants two months of age (Schanler, 1995). The use of pacifiers may have enhanced the efficacy of sucrose more effectively than either intervention on its own. Blass and Watt (1999) examined 40 term neonates undergoing heel lances. Neonates were randomly allocated to receive 2 ml of 12% sucrose alone, water alone, pacifier with water (NNS) or pacifier with 12% sucrose. Pain was measured by cry, facial grimace and heart rate changes. Sucking movements were recorded in real time and quantified during the treatment phase. Sucrose alone diminished cry duration during the heel lance procedure relative to water (8% vs. 50%, $p = 0.003$). Similarly, sucrose was significantly more efficacious than pacifier with water (8% vs. 35%, $p = 0.02$). Sucrose with pacifier was more effective than water with pacifier (5% vs. 35%, $p = 0.001$) or water alone (50%, $p = 0.002$). The pacifier with water was only analgesic when the suck rate exceeded 32 sucks/min. The authors suggested that antinociceptive mechanisms associated with NNS are engaged when sucking thresholds have been reached. The authors further suggested that the orotactile threshold previously described does not have to be reached if orogustatory mechanisms associated with

sucrose taste are activated. Unlike NNS alone, the pain relieving effects associated with sucrose persisted long after the painful stimulus was terminated. The sample size was small, only two groups were blinded, and there was no information about randomization. However, sucrose and NNS in combination was most efficacious for term neonate's pain relief, which is consistent with other similar research.

Carbajal et al. (1999) examined the analgesic effects of intraoral glucose, sucrose and pacifiers for relief of procedural pain in healthy term neonates in a RCT. The researchers reported that NNS was more efficacious than sucrose or glucose. One hundred and fifty term neonates were randomized to one of six groups for a venepuncture: control, 2ml sterile water, 2ml 30% glucose, 2ml 30% sucrose, NNS or 30% sucrose combined with NNS. A newly developed and non-validated behavioral pain score (Douleur Aigue du Nouveau-ne (DAN) (Carbajal et al., 1999) was used as a measure of pain (0 – 10 scale). The 30% glucose and 30% sucrose had similar reductions in pain responses, with median (interquartile) pain scores during venepuncture of 5 (3-7) for 30% glucose and 5 (2-8) for 30% sucrose compared to 7 (5-10) for no treatment and 7 (6-10) for sterile water. NNS alone was more efficacious than either solution alone, with median pain scores of 2 (1 – 4), $p < 0.001$). There was a trend towards lower pain scores in the sucrose and NNS group compared to NNS alone with median pain scores of 2 (1 – 2), $p < 0.06$).

Stevens et al. (1999) examined the combined efficacy of sucrose and NNS for relieving procedural pain in preterm neonates between 27 and 31 weeks of gestation ($n = 122$) in a randomized cross-over trial. Each neonate received all four interventions in random order. For all interventions, the neonate was contained or nested in a SnuggleUp device (Children's Medical Ventures, Inc. Weymouth, MA, #9600N) for 30 minutes prior to the blood test. The SnuggleUp prevented the neonate from engaging in any large body movement. In the control

group, the neonate was contained or nested in a side-lying or supine position during a heel lance procedure, and did not receive a pacifier or other nursing interventions such as stroking, rocking or talking. The three interventions included (a) prone positioning, (b) a pacifier dipped in sterile water or (c) a pacifier dipped in 24% sucrose. Pain was determined using the PIPP (Stevens et al., 1996). Significant differences in PIPP scores between the pacifier with water and control group ($F = 9.00$, $p < 0.003$), and pacifier with sucrose and control group ($F = 24.09$, $p < 0.0001$) were found. There was a trend towards lower PIPP scores with the sucrose and NNS group compared to the water and NNS group ($F = 3.62$, $p < 0.05$). Smaller volumes of sucrose with the provision of NNS may relieve procedural pain in preterm neonates between 27 and 31 weeks gestation. However, containment may have been a co-intervention that further reduced pain responses in all groups and thus minimized the magnitude of group differences. Investigation of the efficacy of these interventions did not include more mature preterm or acutely ill neonates.

Safety

The systematic review and the meta-analysis (Stevens et al., 1997; Stevens & Ohlsson, 1998) provide support for ongoing research for the safety and efficacy of sucrose. Although no adverse effects of sucrose were reported in any study, it is not clear whether the investigators monitored for adverse effects or for how long. Only one study (Willis, Chabot, Radde & Chance, 1977) has hypothesized that 20% sucrose concentrations could predispose preterm neonates to necrotizing enterocolitis (NEC). The authors suggest that the hyperosmolality of sucrose resulted in local trauma to the upper gut wall, which initiated the pathological process resulting in NEC. Small concentrations of sucrose (8 - 12 times per day) in small volumes were delivered directly into the stomach via a #5 nasogastric tube. The sucrose was mixed with calcium lactate. Neonates were non randomly assigned (as determined by the attending physician) to one of three groups; (a) sucrose/calcium lactate given with each feed, (b)

sucrose/calcium lactate given 20 minutes before each feed, and (c) sucrose/calcium lactate dispersed in water given at the end of each feed. Neonates who received sucrose/calcium lactate 20 minutes before each feed were more likely to develop NEC. This study was limited by the lack of demographic data on subjects. It is not clear whether severity of illness, gestational age or the route of delivery, frequency of doses or the hyperosmolality of calcium lactate were the causative factors in the development of NEC. Volumes of 0.5 - 1.0 ml sucrose/calcium lactate in addition to feeds given via a nasogastric tube every two hours may be excessive for preterm neonates. Other pathogenetic mechanisms such as prematurity, alteration of bowel flora and the presence of umbilical lines must also be considered as causative agents for NEC. The osmolality of 24% sucrose is approximately 476 mosmols/L (Stevens & Ohlsson, 1998) compared to commonly administered enteral substances including pregestamil (495mosmols/L) (Jew, Owen, Kaufman & Balmer, 1997). Enteral administration of hyperosmolar substances has been associated with a variety of gastrointestinal problems in neonates, such as NEC, osmotic diarrhea and intestinal ischemia. Compared to many commonly used enteral solutions in the NICU, 24% sucrose is not considered hyperosmolar. However, the osmolality of the solution does not preclude documentation of adverse events.

Summary of the Review of the Literature

There is now sufficient evidence that preterm neonates have physiological (Craig et al., 1993; Field & Goldson, 1984; Grunau et al., 1994a; Perreault et al., 1997; Stevens & Johnston, 1994) and behavioral (Fuller et al., 1990; Lester, 1984; Johnston & Strada, 1986; Mickelsson et al., 1977; Owens & Todt, 1984; Porter et al., 1986; Thoden, Jarvenpaa and Michelsson, 1985) responses to tissue damaging stimuli. The evidence supporting the relationship between painful procedures and future pain responses remains unclear.

Management of procedural pain for neonates has been limited by the misconceptions that preterm neonates do not experience pain. Anand and his colleagues (1987) have provided evidence that preterm neonates have the neurological anatomy and physiological development to perceive and respond to painful stimuli at approximately mid gestation. Many studies have supported Anand et al.'s (1987) findings and indicate that neonates in NICU's are particularly vulnerable to the detrimental effects of pain (Anand, 1990, Anand & Craig, 1996; Carraccio et al., 1996; Fitzgerald, 1991; Fitzgerald & Anand, 1993).

A variety of sucrose concentrations (7.5%, 12%, 24% or 50%), volumes and administration schedules have been implemented to reduce procedural pain in neonates. Sucrose has been shown to calm neonates as early as 9 hours after birth, and the calmness persists 5 - 10 minutes after a painful stimulus (Blass & Ciaramitero, 1994). Various time delays between sucrose intake and the initiation of painful procedures have been used (Blass & Shah, 1995; Stevens et al., 1997; Stevens & Ohlsson, 1998). Reductions in crying time have been found at 2 minutes after sucrose is administered onto the tongue. Two minutes between the time sucrose is administered and the time the pain is experienced appears to be required for taste receptors in the mouth to mediate opioid responses and inhibit nociceptive impulses. When duration of cry is used as an indicator of pain, 0.24g (2ml of 12% weight/volume (w/v) sucrose) is efficacious for heel lances (Bucher et al., 1995; Johnston et al., 1999; Johnston et al., 1997) and venipunctures (Abad et al., 1996) in preterm neonates and heel lances (Blass, 1997; Graillon et al., 1997; Rushforth & Levene, 1993) in term neonates but not for circumcisions (Naqui et al., 1999), eye exams (Pearson, Jorgenson, Blocker, Bauchner & Mirochnick, 1999) or intramuscular injections (Allen et al., 1996). Although there is a trend towards a reduction in crying time with greater concentrations of sucrose (Haouari et al., 1995) no benefits to doses greater than 0.5g have been found (Stevens et al., 1997; Stevens & Ohlsson, 1998).

Sucrose and NNS has been examined as behavioral and environmental approaches to preterm and term neonate pain management. Although the meta analysis (Stevens et al., 1997) suggests that 2 ml of 12 - 24% sucrose, in the range of 0.24g or 0.50g, is effective in reducing pain responses, it is not clear whether the sucrose alone or a synergistic effect of sucrose with NNS is responsible for this effect. In addition, most of the studies included in the meta analysis examined the effects of sucrose on healthy term neonates. Preterm or acutely ill neonates may not tolerate 2 ml of a solution without side effects such as aspiration, bradycardia, tachycardia or desaturations. A few studies (Johnston et al., 1999; Johnston et al., 1997; Stevens et al., 1999; Stevens et al., 2000b) have found very small doses of sucrose (0.12g) reduce composite pain scores comprised of heart rate, respiratory rate and facial expressions in neonates less than 34 weeks of gestation. These smaller doses of sucrose are not efficacious in term neonates and do not appear to be sustained in older neonates. Further research on volume and dose-response for a wide range of neonates is justified.

Development of the Conceptual Framework

Different explanatory models are required to examine effective pain management for preterm and acutely ill neonates. Theoretical explanations of pain, using the Gate Control Theory (GCT) (Melzack & Wall, 1965), existing knowledge of the developing Central Nervous System (CNS), and data on factors that influence neonates' pain responses were used to examine three interventions for eliminating procedural pain in neonates. Within the proposed conceptualization, the painful stimulus was defined as a heel lance. The response to the heel lance was assessed using a composite measure consisting of physiological, behavioral and contextual indicators of pain. The physiological responses were heart rate and oxygen saturation. The behavioral responses included brow bulge, eye squeeze and nasolabial furrow. Gestational age and behavioral state of the neonate prior to the heel lance were contextual

factors that were taken into consideration in the composite pain measure (PIPP) to account for their modifying influence on pain responses.

Gate Control Theory

Melzack and Wall (1965) developed the GCT as an alternative to existing pain theories, such as Specificity Theory (Schiff, 1858; cited by Boring, 1942), that suggested that pain was a straight-line transmission from peripheral receptors to a central pain center. The GCT proposes that pain is not a simple sensory experience but an integration of sensory, affective and cognitive dimensions. According to the GCT, individuals' responses to pain are influenced by internal pain inhibitory mechanisms and external factors such as memories of past painful experiences, culture or expectations of pain (Fields & Basbaum, 1994; Melzack & Wall, 1996; Wall, 1996). Pain is regarded as a multidimensional phenomenon that is unique to each individual. Pain responses are viewed as flexible and influenced by a variety of contextual factors, which further account for the differences in pain responses between and within individuals (Fields & Basbaum, 1994).

The GCT (Melzack & Wall, 1965, 1970, 1996; Wall, 1996) hypothesizes that noxious stimuli initiate a sequence of neural events that converge onto common second-order neurons in the substantia gelatinosa in the dorsal horn. The substantia gelatinosa consists of densely packed cells that extend the length of the spinal cord and act as a gate control system that modulates the synaptic transmission of nerve impulses from peripheral fibers. Modulation of impulses involves the active transformation of impulses from primary neurons to secondary neurons by complex excitatory and inhibitory mechanisms. These mechanisms are referred to as the 'gating mechanism', where the flow of nerve impulses are increased or decreased at the level of the spinal cord. The GCT suggests that large diameter fibers inhibit (close the gate) nociceptive impulses while the small diameter fibers facilitate (open the gate) transmission of nociceptive

impulses. Interventions that compete with small diameter afferent fibers to close the gate, or activate descending endogenous opioid and non-opioid pathways to decrease nociceptive transmission, will decrease pain. Pain impulses involve transduction of nociceptive impulses from peripheral receptors via ascending afferent fibers, transmission of nociceptive impulses to the spinal cord and brain, perception of the stimulus, and modulation of the stimulus by descending inhibitory pathways (see pages 7 – 10). Pain responses occur when neural mechanisms are exceeded or inhibitory mechanisms are ineffective (Wall, 1996).

There is sufficient evidence to support neonates' anatomical and functional capacity to respond to pain (Anand et al., 1987; Anand et al., 1989; Andrews & Fitzgerald, 1994). However, differences in inhibitory mechanisms suggest that developmental factors must be considered when proposing pain-relieving interventions (see page 16). Since preterm and term neonates have sufficient afferent fibers by early gestation, control of pain during procedures may be achieved by providing large, rapidly conducting A-delta fiber stimulation. Similarly, interventions that promote inhibitory mechanisms, in preterm neonates who lack sufficiently developed inhibitory mechanisms (via endogenous opioid and non-opioid pathways), may modulate pain responses.

Although the GCT offers a framework to examine pain and pain-relieving interventions in neonates, further examination of developmental differences between preterm, term and older infants is required. Interventions that are effective in older populations may not be effective for immature neonates. Since pain is an individual experience (Melzack & Wall, 1996), multiple methods of pain assessment are required. In light of a developing CNS, examination of the differences between preterm and term neonates appears to offer a more comprehensive conceptualization of pain.

Developing CNS

The anatomical development of the somatosensory cortex, cerebral cortex, thalamus and hypothalamus are present very early in gestation. Similarly, the sensory fiber development and synapses with interneurons in the dorsal horn of the spinal cord are complete by approximately mid-gestation with functional A-delta and C-fibers to transmit pain impulses (Anand & Carr, 1989, Humphrey, 1964). The hypothalamus-pituitary-adrenal axis that is responsible for maintaining endocrine, autonomic, immunological and behavioral homeostasis is well established by mid-gestation, however, its ability to modulate appropriate pain responses is influenced by gestational age, with the most immature neonates experiencing the least protective responses (Plotsky et al., 2000).

The excitatory neurotransmitters associated with the transmission of pain (including substance P, glutamate and calcitonin gene-related peptide), are present in the dorsal horn neurons by approximately 11 weeks of gestation. The abundance of NMDA receptors during the first few days after birth suggests that pain transmission is increased in neonates compared to adults or older infants, and therefore should be taken into consideration when assessing and managing pain.

There are sufficient data to suggest that pain responses are influenced by gestational age and developmental maturity. Several researchers (Craig et al., 1993; Johnston & Stevens, 1996; Walden, 1997) have reported that pain responses of preterm neonates are similar but significantly less robust than more mature neonates. Results from animal studies provide further indication of how pain responses between preterm and term newborns differ (Anand et al., 1999; Andrews & Fitzgerald, 1994; Coskun & Anand, 2000; Fitzgerald, 2000; Fitzgerald et al., 1988). In general, behavioral responses to pain are less predominant in the immature neonate.

The decreased magnitude of pain responses in preterm neonates, therefore, render this population at risk for inadequate pain management.

Factors Influencing Pain Responses

Behavioral state has been shown to influence neonates' pain responses. Neonates in sleep states are less capable of mounting a vigorous pain response, as evidenced by decreased facial activity associated with heel lances, than neonates in wake states (Gabriel et al., 1981; Grunau & Craig, 1987; High & Gorski, 1985; Stevens, 1993; Stevens et al., 1994). Recognition of gestational age and behavioral state as contextual factors that influence pain response is essential for the present study and included in the composite measure.

Other factors such as severity of illness (Johnston & Stevens, 1996; Michelsson, 1971; Michelsson et al., 1983; Stevens et al., 1994), frequency of prior painful procedures (Johnston et al., 1993; Johnston & Stevens, 1996; Stevens et al., 1999), postnatal age (Johnston et al., 1996), duration of hospitalization in NICUs (Grunau et al., 1994a; Grunau et al., 1994b), time interval between last painful procedure (Franck, 1986; Johnston & Stevens, 1996) and invasiveness of the painful procedure (Porter et al., 1999) have all been associated with influencing neonates' physiological and behavioral responses to pain.

Environmental factors such as light, noise, and frequency of handling have also been shown to reduce stress responses by reducing the cumulative stimuli the neonate experiences (Als et al., 1986; Als et al., 1994; Buehler, Moser & Von Siebenthal, 1995; Fleisher Vandenberg, Constantinou et al., 1995). Although these studies included small sample sizes, and outcomes were not blinded, the results suggest that environmental factors may influence pain response but further research is required.

Some studies (Guinsburg et al., 2000; Zeichner et al., 2000) have indicated that behavioral and physiological pain responses are more evident in females, while other studies

(Grunau & Craig, 1987) have suggested that male neonates show increased behavioral pain responses. Christy, Pichichero, Reed and Decker (1995), Gonsalves and Mercer, (2000), and Stevens et al. (1994) found no effect of gender on pain responses. The inconsistencies in the findings indicate the need for further research examining the influence of these factors on neonates' pain responses.

Summary of Conceptual Framework

Within this conceptualization, three interventions for eliminating procedural pain were hypothesized to function at two separate levels: (a) the interventions alter the flow of nociceptive impulses at the afferent fibers (via large diameter fibers) and (b) the interventions stimulate the release of inhibitory neurotransmitters at the level of the spinal cord (through the release of endogenous opioids and increased serotonin uptake). The mechanisms underlying sucrose and NNS are different, however, theoretical mechanisms of the pain relieving interventions will be examined in light of the proposed conceptual framework.

Based on Melzack and Wall's (1965, 1970, 1996) and Wall's (1996) assumptions of pain sensation and an understanding of neuroanatomical and neurochemical development that are influenced by a variety of factors, one could examine the efficacy of sucrose and NNS for procedural pain relief in preterm neonates of varying gestational ages. The proposed conceptual framework offers a possible explanatory mechanism to explore the efficacy of pain management interventions. Furthermore, the proposed framework may provide information to clarify how preterm neonates' responses to pain management interventions differ with respect to gestational age. Factors that may affect physiological and behavioral pain responses such as frequency of painful procedures, postnatal age, severity of illness, time since last painful procedure and gender will be examined in the present study. Other factors such as environmental light, noise, maternal antenatal therapy and infant steroid therapy (Grunau, Oberlander, Whitfield, Fitzgerald

& Lee, 2001), and care-giving activities are beyond the scope of this research but should be considered in future research. Similarly, factors within the GCT that influence pain and responses to pain-relieving interventions, such as memory of previous pain experiences, culture or expectations of pain are not feasible with neonates and therefore were not included in the present study. Awareness of these factors, however, may provide direction for future research.

Chapter III

METHODOLOGY

Purposes

The main purpose of this study was to compare the efficacy and safety of three approaches of eliminating procedural pain in neonates. The ultimate goal was to contribute to the body of knowledge on the management of procedural pain in neonates and provide evidence for clinical guidelines and evidence based practice and research.

Research Questions

Primary Question

1. For term and preterm neonates undergoing a heel lance, is 0.5mls of 24% sucrose delivered via a syringe onto the anterior portion of the neonate's tongue immediately followed by the insertion of a pacifier into the neonate's mouth, more efficacious than:
 - (a) 0.5mls of 24% sucrose delivered via a syringe without a pacifier; or
 - (b) 0.5mls of sterile water delivered via a syringe with a pacifier.

Secondary Question

2. For term and preterm neonates undergoing a heel lance, is 0.5mls of 24% sucrose, delivered via a syringe onto the anterior portion of the neonate's tongue immediately followed by the insertion of a pacifier into the neonate's mouth, safe compared to:
 - (a) 0.5mls of 24% sucrose delivered via a syringe without a pacifier; or
 - (b) 0.5mls of sterile water delivered via a syringe with a pacifier.

Exploratory Questions

3a). Is there an association between gestational age, and efficacy and safety of sucrose for term and preterm neonates undergoing a heel lance?

3b). Are there differences in neonates' physiological and behavioral indicators of pain in the sucrose and NNS, sucrose alone and water and NNS groups for each phase of the heel lance procedure?

Operational Definitions

Pain was defined as the neonate's physiological and behavioral responses to a tissue-damaging stimulus within the context of gestational age and behavioral state. The nature of these responses depended on the neurobehavioral and physiological maturity associated with each developmental stage or gestational age. Pain was measured using the PIPP (Stevens et al., 1996) (refer to page 62 for a full description of the PIPP).

Gestational age (in weeks) of the neonate was determined by the most accurate method available in the following order: (a) ultrasound prior to 13 weeks gestation or (b) the number of weeks from the mother's last menstrual period. If more than one method was available, the ultrasound was used to determine gestational age.

Neonate was defined as any infant admitted to the NICU within the first 28 days of life.

Heel lance was defined as an invasive tissue damaging procedure performed with an automated lancet (Becton Dickinson, microtainer, 2.2mm, #365759) to the medial or lateral aspect of the neonate's heel to obtain blood for laboratory testing. A minimum of 0.2 ml's of blood was required and involved lancing and squeezing of the heel.

Sucrose was defined as a 24% disaccharide solution prepared under sterile conditions by the research site (e.g. pharmacy department). The solution was intended for the management of procedural pain in study neonates. The dose (in grams) was calculated by the concentration (%) of sucrose by the volume (ml) delivered to the neonate. Based on the physiological status of preterm neonates in NICU's, a dose of 2 ml of sucrose was not feasible. For the purpose of this study an alternative dose, which considers preterm neonates' developmental stage and predisposition for NEC, will be 0.5 ml or 0.12grams (which is one half of the recommended dose derived from the meta analysis) (Stevens et al., 1997).

Nonnutritive Sucking was defined as a "Wee Soothie" pacifier (Children's Medical Ventures, Inc. Weymouth, MA, #9600N) introduced into the neonate's mouth. Sucking was encouraged by gentle, rhythmic stimulation of the pacifier by the research assistant.

Severity of Illness was defined and measured using the Score for Neonatal Acute Physiology (SNAP: PE), a measure comprised of physiological indicators as well as laboratory tests and vital signs (refer to page 64 for description of the SNAP: PE).

Study Design

A randomized controlled trial (RCT) with prognostic stratification for gestational age (a) 27 - 31 ⁶/₇ weeks; (b) 32 - 35 ⁶/₇ weeks; and (c) up to 43 weeks, was used to answer the research questions. The target population consisted of all neonates in a Metropolitan university affiliated NICU.

Sample

Inclusion Criteria

All neonates hospitalized in a NICU who:

1. Were (a) ≥ 27 weeks gestation at birth; and
(b) ≤ 7 days post natal age;

2. Had 5 minute Apgar scores ≥ 7 or cord pH (arterial or venous) ≥ 7.0 ;
3. Had not undergone surgery

Exclusion Criteria

All neonates hospitalized in a NICU who:

1. Had a diagnosed major congenital disorder (e.g. neuromuscular disease, spinal cord injury) that may interfere with the neonate's ability to respond to procedural pain;
2. Had received analgesics or sedatives within 12 hours of enrolment;
3. Were receiving paralytic agents (e.g. pancuronium);
4. Had parents who did not speak English and did not have someone who could translate from their language into English and back.

Sample Size Calculation

The primary outcome of pain response was used to calculate sample size. One prior study that used PIPP scores indicated that the mean pain score from a heel lance decreased from 9.81 (SD = 3.50) to 7.89 (SD = 3.30) in a control versus a pacifier with sucrose group, using a significance level of 0.009 to account for multiple comparisons (Stevens et al., 1999). A second study reported a significant reduction of PIPP scores from 8.30 (sterile water) to 6.70 (single dose of 0.05 ml 24% sucrose) and 5.40 (triple dose of 0.05 ml 24% sucrose) ($F = 9.14$, $p < 0.001$) (Johnston et al., 1999). Given these data, a reduction of 2 points on the PIPP score (approximately 20% on mean observed scores) was considered clinically significant. Using a two-tailed test, a standard deviation of 3.5, an alpha of 0.05 and a power of 80%, the sample size required to detect a reduction of 2 points in PIPP scores between the three interventions was **186** (62 neonates per group). An estimated 10% missing data rate was expected due to equipment failure or inability to visualize facial actions secondary to medical equipment (i.e.

endotracheal tube). Therefore, the sample size was adjusted to 205 to account for the possibility of missing data.

RCT Procedure

Prior to Recruitment

The proposal was presented at the research site and the purpose, data collection procedure, interventions, outcome measures, procedures of the RCT maneuver, contamination, co-intervention and losses to follow up were addressed with the staff. The intervention was piloted with a convenience sample of 6 neonates to determine the feasibility of the measure, design and data collection strategy in the research site. No major changes were made.

Maneuver

Potential participants in the NICU were identified by the nurse in charge of the NICU using a copy of the inclusion criteria that was provided by the investigator. Parents of infants who met the inclusion criteria were approached by the charge nurses as soon as possible after admission to the NICU and asked if they were willing to listen to an explanation of the study. If they agreed to be approached, the investigator was contacted and given their names and location. She then explained the study and obtained consent to participate (Appendix C). An information letter was attached to the neonate's bedside to inform medical and nursing staff that the neonate was enrolled in the study. The next scheduled blood test after consent had been sought was performed by the investigator or her designated replacement (registered respiratory therapist). Non-consenting parents were asked for permission to collect neonate and maternal demographic data to determine representativeness of the sample. A chart abstraction sheet was used to collect demographic data (Appendix D). All baseline characteristics from participating neonates were collected prior to randomization.

The randomization procedure for all participating neonates was determined prior to the study from a centrally controlled, computer generated table of random numbers, which was concealed from the investigator. Separate randomization tables were used for each gestational age stratum to ensure equal distribution of neonates of differing gestational ages within intervention groups. The randomization schedule was given to the research pharmacist prior to study commencement. Immediately prior to the scheduled blood test, the research pharmacist randomized the neonate to one of three groups: (a) sucrose and NNS, (b) sucrose alone or (c) sterile water and NNS. Based on the literature to support the use of sucrose and/or NNS, it was considered unethical to deny neonates a form of treatment. Therefore, sterile water and the provision of NNS was used for the control group. Because of the study design and intentional lack of a control group (i.e. sterile water alone or no treatment), blinding of the intervention was only possible for the two groups who received a pacifier. Both sucrose and sterile water were prepared by the research pharmacist under sterile conditions and drawn up in a tuberculin syringe and labelled as “study drug”. Both solutions were clear and non-odorous and not visibly distinguishable in any other way.

All neonates received one of three interventions as defined by the group to which they were randomized. Every attempt was made to perform the heel lance immediately after randomization had occurred to standardize the research protocol across neonates and minimize the effects of prior painful procedures. Prior to the heel lance, all neonates were placed in a supine position with their legs slightly flexed towards the chest. The investigator performed all but five (97.4%) of the heel lances at the neonate's bedside. One other person (registered respiratory therapist) performed the remaining heel lances.

The phases of the heel lance procedure included:

(1) Baseline: The neonate was continuously monitored and videotaped for 60 seconds.

(2) Intervention: The neonate received one of the three solutions.

(3) Warming: The neonate's foot was warmed with a cotton cloth for 120 seconds. During the 120 seconds, neonates randomized to receive a pacifier were encouraged to suck by gently moving the pacifier in and out of the mouth. After 120 seconds, the foot was unwrapped and wiped with an alcohol swab.

(4) Lance: The lateral or medial aspect of the neonate's heel was lanced with an automated lancet (Becton Dickinson, microtainer, 2.2mm, #365759) and the investigator waited 15 seconds.

(5) Squeeze: After 15 seconds, the neonate's heel was gently squeezed until sufficient blood was collected. The initial squeeze phase was 15 seconds after the heel lance and subsequent squeeze phases, if required, were divided into 30-second intervals.

(6) Return to baseline: The neonate was monitored for 5 minutes after the procedure.

Figure 1. summarizes the heel lance procedure.

Figure 1. Heel Lance Procedure by Phase.

Figure 1. The first *PIPP score was computed at 210 seconds and the second **PIPP score was computed at 240 seconds.

Neonates Randomized to the Sucrose and NNS Group

Neonates in the sucrose and NNS group received 0.5 ml of 24% sucrose via a syringe onto the anterior surface of the tongue followed immediately by the insertion of a Wee Soothie

pacifier (Children's Medical Ventures, Inc. Weymouth, MA) into the neonate's mouth. The pacifier was held in place by the investigator or a research assistant as required 2 minutes before, during and 5 minutes following the heel lance.

Neonates Randomized to the Sucrose Group

Neonates in the sucrose group received 0.5 ml of 24% sucrose via a syringe onto the anterior surface of the tongue 2 minutes prior to a heel lance. No pacifier was offered.

Neonates Randomized to the Water and NNS Group

Neonates in the water and NNS group received the identical intervention as neonates randomized to the sucrose and NNS group except that they received 0.5 ml of sterile water instead of 24% sucrose.

Outcome Measures

Pain Response and Safety

Pain Response

Pain was measured using the PIPP (Stevens et al., 1996) (Appendix B). The PIPP was developed in response to the lack of a valid measure of pain for research and clinical practice. The instrument was specifically developed for preterm neonates and term neonates, and includes the physiological, behavioral and contextual indicators that have been shown to be most consistent with neonates' pain responses across many research studies and situations (Stevens, Johnston and Gibbins, 2000a). A summary of the psychometric properties of the PIPP is included in Appendix E.

In the PIPP, the physiological indicators of pain include the change from baseline in maximum *heart rate* within 30 seconds following an acute painful stimulus and the change from baseline in minimum *oxygen saturation* within 30 seconds of a painful stimulus. The behavioral indicators of pain include the change from baseline in *brow bulge*, *eye squeeze* and *naso-labial*

furrow. The contextual indicators of pain include *behavioral state* at baseline and *gestational age* at the time of data collection. Behavioral state is assessed using Grunau and Craig's (1987) adaptation of Prechtl's (1974) observational rating system of sleep/wake states. The states included: (1) quiet sleep; as evidenced by closed eyes and no eye movement to (2) active sleep; as evidenced by closed eyes and rapid eye movement to (3) quiet awake; as evidenced by open eyes and no eye movement to (4) active awake; as evidenced by open eyes and eye movement.

Indicators in the PIPP are numerically scored. Four point scales (0, 1, 2, 3) reflect the changes in the increasing magnitude in the indicators from baseline values. The scores obtained for the seven indicators are summed for a total pain score. The total number of PIPP scores calculated is dependent on the duration of the intervention (minutes) as well as the completeness of the physiological and behavioral indicators. The maximum attainable score is dependent on gestational age and behavioral state. For extremely immature neonates in quiet sleep states, the total possible score is 21, as gestational age and sleep state are each assigned a score of 3. In contrast, neonates greater than 36 weeks gestation are assigned a score of 0 for gestational age. Therefore, the maximum possible PIPP score for the most mature neonate, even during sleep states, is 18. Gestational age and behavioral states are weighted to account for developmental differences in preterm and term neonates' abilities to respond to pain. For all neonates, a score of less than 6 is considered to reflect minimal pain and a score greater than 12 indicates moderate to severe pain. However, further research to determine whether the values of 6 and 12 are sensitive cut-off points for minimal versus moderate-severe pain for each gestational age group is required. The mean pain score for preterm neonates' pain associated with heel lances with a standard care intervention has been reported as 9.8 (Stevens et al., 1999).

The PIPP has been shown to have face and content validity and evidence of beginning construct validity for pain measurement of preterm neonates of various gestational ages. Walden

(1998) examined the internal consistency and construct validity of the PIPP for preterm neonates born at 24 - 26 weeks gestation and studied at 27 - 32 weeks PCA. PIPP scores were evaluated during a painful (heel lance) and non-painful (diaper change) situation. Significant differences between events across all PCA were found ($p < 0.004$). In regards to internal consistency, brow bulge and eye squeeze contributed significantly to total PIPP scores. Behavioral state showed significant positive item-total correlations ($r = .59-.76$).

In a randomized cross-over design (RCT) to assess the clinical validity of the PIPP in preterm infants undergoing a heel lance, Ballantyne, Stevens, McAllister, Dionne and Jack. (1999) found that PIPP scores were significantly higher for painful events (11.00 ± 1.3) compared to non-painful baseline data (4.9 ± 1), ($F = 48$, $p = 0.0001$). Both inter ($\alpha = 0.93 - 0.94$) and intra ($\alpha = 0.94 - 0.98$) rater reliability were high. These data suggest that the PIPP is a reliable and sensitive measure of pain for preterm neonates. For a more in-depth discussion of instrument development and initial validation see Stevens et al. (1996) and Appendix E.

Safety

Safety was measured by determining the nature and incidence of adverse events.

Adverse events were defined as:

- (a) Choking, coughing or vomiting following the administration of sucrose
- (b) Sustained tachycardia (heart rate > 200) or bradycardia (heart rate < 80) for > 15 seconds following the administration of sucrose
- (c) Sustained tachypnea (respiratory rate > 80) or dyspnea (respiratory rate < 20) for > 15 seconds following the administration of sucrose
- (d) Sustained oxygen desaturation $< 80\%$ for > 15 seconds following the administration of sucrose

The safety criteria were attached to each neonate's medical record and any adverse effects were recorded.

Other Outcomes

The Score for Neonatal Acute Physiology SNAP: PE The SNAP: PE is a measure of severity of neonatal illness (Richardson, Gray, McCormick, Workman and Goldman, 1993; Richardson, Phibbs et al., 1993). The SNAP: PE is comprised of indicators including birth weight, Apgar score at 5 minutes, and small for gestational age, as well as 26 items based on laboratory tests and vital signs. The degree of physiologic instability is given a weighted score of 0 to 5 points. The SNAP: PE is highly correlated with other indicators of illness including nursing workload ($r = 0.59$), therapeutic intensity ($r = 0.78$), physician estimates of mortality risk ($r = 0.65$) and length of stay ($r = 0.59$) (Escobar, Fischer et al. 1995; Richardson et al., 1993; Richardson and Escobar, 1998; Richardson, Corcoran, Escobar & Lee, 2000). The SNAP: PE has been validated on over 27,000 infants in 31 NICUs in Canada and the USA (Richardson et al., 1993) and has been used in previous studies using the PIPP.

Data Collection Procedure

Data were collected by obtaining demographic information from the neonate's medical and nursing records prior to randomization using a chart abstraction sheet (Appendix D) that had been used previously in other studies (Stevens et al., 1999) and was pilot tested in this study. Prior to the heel lance, the neonate's behavioral state, baseline heart rate and oxygen saturation were recorded. An oxygen saturation monitor (Pulse Oximeter, Model N-3000, Hayward, CA) was applied to the neonate's hand or foot to record the heart rate and oxygen saturation. The physiological indicators of pain were recorded by using a SATMASTER data collection system (EMG, Los Angeles, CA) that provides descriptive statistics for each phase of the heel lance procedure. The behavioral indicators of pain were recorded on videotape with a zoom lens (Sony digital zoom, handycam vision, 72X). Phases of the heel lance procedure were

indicated on the videotape by verbal commands using letters. The use of letters maintained the facial coder's blinding to the phases of the heel lance procedure.

After data collection was complete, all study equipment was removed and the neonate was repositioned into a developmentally supportive position with legs tucked up towards the chest and arms positioned towards midline. Raw physiological data from each neonate was copied from the personal computer and sent to the investigator for data reduction, coding and analysis. All data forms were double checked for consistency and completeness of information by an independent nurse researcher. Any missing information was obtained by the investigator through health records to complete all data forms. The PIPP scores were manually computed from the raw physiological data and facial coding. The calculation of all PIPP scores were double checked by two research assistants and double entered into a data management system by two separate research assistants blinded to group allocation. Logic checks were performed on the individual databases and reviewed by the research assistants for any errors. After logical errors were corrected, the two databases were compared using a Microsoft Excel program to determine discrepancies.

Physiological data were sampled at 100Hz and recorded second by second. Signals, digitalized in the Pulse Oximeter, were transmitted into a personal computer on site. All phases of the heel lance were recorded on the computer with electronic event markers that were synchronized with the verbal commands using letters on the videotapes. If the neonate did not have a pulse oximeter as part of routine care, a consistent monitor used for all study neonates was applied to the foot or the hand for the purpose of the study. For each data collection session, the investigator calibrated the neonate's EKG monitor with the pulse oximeter and the SATMASTER system (EMG, Los Angeles, CA). If there was a discrepancy in the recorded heart rates (of greater than 10 beats/minute) between the two monitors (detected by the research assistant at the time of data collection), the data were collected manually by the research assistant using a preprinted and standardized form with 5 second time increments. Manual calculation of maximum and minimum as well as mean and standard deviations of heart rate and

oxygen saturation for each phase were computed by the investigator at a later time and then entered into the database for analyses. Manual calculation was required for eight neonates (4% of the sample). Three neonates were randomized to the sucrose and NNS group, one neonate was randomized to the sucrose alone group and four neonates were randomized to the water and NNS group.

Behavioral data were videotaped in real time, copied and forwarded to a facial coder who had been specially trained in facial coding and who was kept uninformed to the purpose of the study, phases of the heel lance procedure and group allocation (in the case of the two pacifier groups). Intra-rater reliability with the facial coder had been established in previous studies by having the facial coder independently code facial behaviors during painful and non-painful events ($\alpha = 0.89-0.91$). The videotaped facial actions for the current study were coded with a second to second analysis. Intra-rater reliability between facial coding was established by scoring and re-scoring 10 randomly selected heel lance sessions. Reliability was re-established after every 25 neonates were entered into the study. The frequency of reliability checks was arbitrarily determined prior to the start of the study. If more than 10% of the behavioral data was not able to be coded by the facial coder, due to inability to visualize facial actions (e.g. neonate turned head, equipment covered eyes or mouth), the data were considered missing and that neonate was excluded from the analyses. Missing behavioral data were only detected by the facial coder at the time of analyzing and coding the videotapes.

Threats to Internal Validity

Although many potential confounders were controlled for by the RCT design, threats to the internal validity included the number of invasive procedures performed between the neonates' birth and the data collection. Attempts were made to recruit and randomize neonates as soon after birth as possible, and every attempt was made to collect data immediately after randomization. The primary outcome, pain, was determined by using a validated measure and the coding and analysis of the data were done by individuals who were blinded to two treatment intervention solutions and who were kept uninformed as to the study purpose. The criteria for

assessing safety were determined using standardized and accepted definitions.

The stimulus (heel lance), the procedure and the automated lancet were consistent throughout the study period; however, the use of pacifiers at other times in the NICU was not controlled for due to ethical consideration. Although the investigator does not feel that her behavior was different with the group of neonates who did not receive pacifiers, there is no way to be certain.

Recruitment

To maximize recruitment with the RCT, the investigator visited and/or contacted the research site on a daily basis. The investigator was also available to answer any questions the staff may have had about the study via pager at any time.

Blinding

Sucrose and sterile water were provided by the NICU pharmacy department and double-checked by two pharmacists prior to dispensing. The tuberculin syringe had the pre-loaded volume of 0.5mls solution. Both solutions were clear, non odorous and had similar textures. Immediately prior to the scheduled time for the blood test, the neonates were randomized by the research pharmacist using the predetermined randomization table. The syringe was delivered to the investigator or her designated replacement who performed the heel lance. Due to ethical concerns already discussed, the investigator and research assistants were only blinded to the two pacifier groups.

Data Analysis

Interim Analysis

A safety monitoring committee consisting of a Neonatologist, Epidemiologist and Clinical Nurse Specialist/Neonatal Nurse Practitioner was set up before the trial began. The chair of the safety monitoring committee (Neonatologist) was informed of each adverse event as per unit policy. For each adverse event, the Neonatologist reviewed the neonate's clinical status in relation to the event and examined the need for an interim analysis. If an interim analysis had

been deemed necessary by the neonatologist, stopping rules for the current study would have been employed as necessary. The stopping rules included the occurrence of adverse events of a major nature directly related to the study intervention including: (a) severe choking, coughing or vomiting following the administration of solution, or (b) tachycardia or bradycardia which requires immediate medical intervention such as intubation or resuscitation. The total number of adverse events would have been compared to the incidence of this type of event in non study patients after approximately every 50 patients by the safety monitoring committee. Although there were six adverse events during the study period, they were not considered major adverse events and therefore, no interim analysis was performed.

Final Analysis

The raw data were first reduced and coded prior to the final analysis. The physiological data from the personal computer were summarized using the SATMASTER software program (EMG, Los Angeles, CA). Descriptive SATMASTER statistics provided means, ranges and variances of the heart rate and oxygen saturation indicators for each phase of the heel lance procedure. The behavioral data from videotapes were analyzed second-by-second by a trained coder and the percentage of facial actions for each phase was manually computed to provide detailed analysis of behavioral pain indicators.

Representativeness of the sample was first determined by comparing data from the eligible refusers (whose parents gave consent) to those neonates who participated in the study. Later, representativeness of the sample was made by comparing the study sample to the annual statistics from the study hospital's 1999 perinatal database that was verified with the administrative program director for accuracy. The hospital's perinatal database included all live births including neonates recruited into the study.

Demographic and other baseline variables prior to randomization were compared between treatment groups and descriptive statistics were calculated. Although more multiple births were found in the least mature age stratum, there are no data to suggest that pain responses are related to genetic factors, therefore, pain responses from multiple births were considered independent of each other. Descriptive statistics were used to analyze data for normality and to determine if the data met criteria for parametric tests. Nominal, categorical and ordinal data were obtained from the chart abstraction sheet (Appendix D); interval data were obtained from the PIPP scores; and categorical data were obtained from the safety criteria.

The distribution of PIPP scores was examined by producing a normal probability plot. The observed values plotted against the expected values of all variables approximated linearity. Homogeneity of variance was used to test the assumption that the variances between the three intervention groups were not statistically significant. The results were not significant (Levene Statistic 2.09, $p = 0.13$), therefore decreasing the risk of Type 1 errors (Tabachnick & Fidell, 1989).

The primary question of the study was to determine the most efficacious method of sucrose delivery for neonates experiencing a heel lance. A one-way analysis of variance (ANOVA) was performed to determine how the primary outcome, PIPP scores, changed by intervention group at 30 seconds following the heel lance. A second PIPP score was computed at 60 seconds (data from 30 – 60 seconds post heel lance) to determine the efficacy of the interventions at a later time. For significant ANOVAs, comparisons using Tukey Honestly Significant Difference tests were conducted to determine where the differences were found (Norman & Streiner, 1994).

The secondary research question was to determine the nature and incidence of adverse effects by treatment group: sucrose and NNS, sucrose alone or sterile water and NNS. Due to the

small number of adverse events, only frequencies and percentages of adverse events by phase were calculated.

The first exploratory question examined the association between gestational age and efficacy and safety of sucrose for term and preterm neonates. Within each gestational age stratum, ANOVAs were performed to determine how PIPP scores changed by intervention group. For significant ANOVAs, post hoc Tukey tests were conducted to determine significant differences within levels of the factors. The second exploratory question explored the differences in neonates' physiological and behavioral indicators of pain in the sucrose and NNS, sucrose alone and water and NNS groups for each phase of the heel lance procedure. A one-way ANOVA to determine how the indicators changed by intervention group was performed. For significant ANOVAs, post hoc Tukey tests were conducted.

A hierarchical multiple regression model was used to explain variation in PIPP scores. Dummy variables were used to indicate categories for gender, intervention group and delivery type. Variables were entered sequentially into the model depending on their potential for contributing to the variance in PIPP scores. Residual plots were examined for appropriateness of the linear model and Durban-Watson statistics were used to test for the presence of correlation in the regression residuals (Norusis, 1993). No correlation between residuals was found. The level of significance for all tests was retained at 0.05.

Ethics

Written approval was received from the joint committee of the University of Toronto and the Hospital For Sick Children and the participating institution. All parents of neonates who met eligibility criteria were approached regardless of age, gender, socioeconomic status or racial/ethnic background. Every attempt was made to approach and communicate with all parents of eligible infants. Parents who were interested in the study were assured of their right to

withdraw their participation from the study at any time and were told that their decisions would not have had any repercussions to the care that they or their neonate had received. A written copy of both the study's explanation and the consent form (Appendix C) were given to each consenting parent. All consent forms will be locked in a cabinet and kept on file separate from the data for a minimum of seven years.

Following all data collection, the documents were collected and maintained by the investigator and secured in a locked office. Confidentiality was ensured by the use of code numbers corresponding with the names of the respondents. The investigator kept a master list linking code numbers to identifying data in a locked cabinet separate from the consents and data. Parents were informed that there were no known risks from participating in the study but possible benefits included improved pain management for neonates undergoing a heel lance. Parents were free to remove their neonate from the study at any time.

Parents were informed that the results of the study would be published and presented. It was explained to parents that data would not disclose their personal identities as they will be presented in aggregate form. Group results of the study will be made available to parents of neonates who participated in the study, on request.

Chapter IV

RESULTS

This chapter is divided into four sections. In the first section, the descriptive characteristics of the study sample are described. In the second section, the representativeness of the study sample is examined. In the third section, the results of the primary analyses for each of the research questions are reported. The fourth and final section includes a secondary analysis, including a regression model, that outlines the variables contributing to the variability in PIPP scores to determine other variables that may contribute to pain responses.

Descriptive Characteristics of the Study Sample

Of the 1061 neonates who were admitted to the NICU during the study recruitment period (21/05/1998 – 23/09/1999), 661 neonates met the inclusion criteria. However, 452 neonates were not recruited for the study because (a) they were missed by the investigator or research assistant, (b) the investigator, research assistant or equipment were not available for data collection, or (c) a specific age stratum was required. The last stratum to complete enrolment was stratum 1 (neonates born between 27 and 31 6/7 weeks of gestation). Therefore, during the time that only neonates within stratum 1 were required, eligible neonates in the other two strata were not recruited.

Seven (3.3%) of the parents who were approached for the study declined participation, leaving 202 neonates whose parents agreed to the study. Another 6.7% (n=12) of the neonates were eliminated from analysis because more than 10% of physiological and/or behavioral data were missing (due to equipment failure). Recruitment was stopped after 202 neonates because the sample size required to detect a 2-point difference in PIPP scores ($n = 186$) between treatment groups was met and the gestational age strata had similar sample sizes. One hundred

and ninety neonates remained in the sample and were used in the data analysis. Figure 2. summarizes the recruitment of the sample.

Figure2. Recruitment of the Study Sample

Representativeness of the Study Sample

The Refusers

The most commonly cited reason for study refusal was “no interest in research” ($n = 5$). The two other reasons for study refusal were no interest in giving sucrose to their neonates ($n = 1$) and no interest in giving a pacifier to their neonates ($n = 1$). Parents who refused to participate were asked for permission to gather information from their neonates' medical records. All parents agreed and the data from the refusers were compared with the participants (Table 3).

The number of parents who refused participation was small ($n = 7$). Differences between refusers and participants were noted in gestational age, birth weight, gender or severity of illness as measured by SNAP: PE scores, although these were small and not considered to be clinically important. The findings suggest that the neonates whose parents refused participation in the study were similar in gestational age and gender, but were slightly larger and less acutely ill, as measured by the SNAP: PE score, than neonates who participated in the study.

Table 3

Comparisons of Study Participants and Refusers

Variable	Participants ($n = 190$) mean (SD)	Refusers ($n = 7$) mean (SD)
Gestational age (weeks)	33.7 (3.80)	33.7 (3.80)
Birth weight (grams)	2244 (952.33)	2432 (980.30)
SNAP: PE score (range 0 - 183)	4.27 (5.50)	3.88 (4.90)
# male	94 (49%)	2 (28%)

Comparisons of Maternal and Neonate Characteristics

In this study, neonates were recruited from one NICU in a large Metropolitan teaching hospital. To determine how representative these neonates were of the population they were recruited from, a comparison was made between the sample and the annual report released from the hospital's 1999 perinatal database. All data from the perinatal database were confirmed by the administrative program director for accuracy. This comparison is not ideal, as the study subjects were included and accounted for 5% of the total database, and could not be identified within the group. However, this comparison was the best comparison possible. Table 4 summarizes the neonatal and maternal characteristics in the study sample and the hospital's 1999 perinatal database.

Comparisons of Study Participants and "losses to follow up"

The number of neonates who were lost to follow-up was small ($n = 12$). These neonates were randomized and received one of the three interventions. However, it was not known at the time of data collection that the video equipment had malfunctioned and all behavioral data were lost. In order to determine representativeness between the study participants and the neonates who were lost to follow-up, a comparison of demographic data was made. No differences between study participants and losses to follow-up were found. Table 5 summarizes the neonatal characteristics in the study sample and the losses to follow-up.

Group comparisons at randomization.

The three intervention groups were similar at the time of randomization. Table 6 contains a description of neonatal attributes at study entry, Table 7 contains frequencies of neonatal attributes at study entry and Table 8 contains the frequency of painful procedures at the time of study entry.

Table 4

Comparison of Neonatal and Maternal Characteristics in Sample and 1999 Perinatal Database

Variable	Research Sample (n = 190) n (%)	Perinatal Database (n = 3679) n (%)
<u>Neonate</u>		
Parity		
Singleton pregnancy	112(59)	2477 (67)
Sex		
Male	94 (49)	1972 (53)
Apgar		
5 minute >7	180(95)	3605 (98)
<u>Maternal</u>		
Type of Delivery		
Vaginal	110 (58)	2829 (77)
with epidural/spinal anesthesia	73 (65)	1925 (68)
no epidural	36 (34)	557 (20)
other	1 (0.50)	347 (12)
Caesarean Section	80 (42)	850 (23)
under epidural/spinal anesthesia	73 (91)	805 (95)
under general anesthesia	7 (9)	45 (5)

Table 5

Comparisons of Study Participants and Losses to Follow Up

Variable	Participants (n = 190) mean (SD)	Losses (n = 12) mean (SD)
Gestational age (weeks)	33.70 (3.80)	33.76 (3.16)
Birth weight (grams)	2244 (952.33)	2146 (819.21)
SNAP: PE score (range 0 - 183)	4.27 (5.50)	5.12 (3.82)
# male	94 (49%)	5 (42%)

Table 6

Description of Neonate Attributes at Study Entry

Variable	Sucrose & NNS (n=64)		Sucrose (n=62)		Water & NNS (n=64)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Gestational age at birth (weeks)	33.69 (3.84)	27 - 41	33.9 (3.83)	27 - 41	33.67 (4.05)	27 - 42
Birth weight (grams)	2207(924)	934 - 4280	2286(1002)	614 - 4760	2242 (943)	905 - 4090
Age at enrolment (days)	3.12 (1.85)	1 - 7	3.02 (1.75)	1 - 7	2.67 (1.89)	1 - 7
Weight at data collection (grams)	2128 (956)	715 - 4280	2216(1010)	600 - 4620	2143 (951)	885 - 4070
SNAP-PE score (0 - 183)	4.14 (4.56)	0 - 17	4.68 (6.73)	0 - 40	4.00 (5.02)	0 - 20
Time since last feed (hours)	2.14 (1.41)	0 - 6	2.25 (1.79)	0 - 8	2.17 (1.77)	0 - 10
1 minute Apgar (0 - 10)	8.44 (0.96)	1 - 9	8.53 (0.78)	1 - 9	8.48 (0.96)	2 - 9
Time since last painful procedure (hours)	9.12 (6.40)	1 - 23	8.09 (6.00)	1 - 23	8.75 (5.75)	1 - 23

Table 7

Frequency of Neonate Attributes at Study Entry

Variable	Sucrose & NNS (n=64) N	Sucrose (n=62) N	Water & NNS (n=64) N
Gender			
Male	30 (47)	32 (51)	32 (50)
Type of delivery			
Spontaneous vaginal	32 (50)	27 (45)	37 (58)
Vaginal & Vacuum	4 (6)	1 (1)	2 (3)
Forceps assisted	1 (1)	1 (1)	4 (6)
Breech	0 (0)	1 (1)	0 (0)
Caesarean	27 (42)	32 (52)	21 (33)
Type of analgesia			
None	12 (19)	10 (16)	14 (22)
Epidural	51 (79)	48 (77)	47 (73)
General	1 (1)	3 (5)	3 (5)
Other	0 (0)	1 (1)	0 (0)

Table 8

Frequency of Painful Procedures at Study Entry

Variable	Sucrose & NNS (n=64)		Sucrose (n=62)		Water & NNS (n=64)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Heel lances	5.27 (3.19)	1 – 16	5.11 (3.75)	0 – 17	5.42(4.33)	0 - 20
Venous sticks	2.16 (2.22)	0 – 13	1.92 (1.63)	0 – 6	1.91 (1.88)	0 - 7
Arterial sticks	0.23 (0.58)	1 – 3	0.23 (0.46)	0 – 2	0.33 (0.88)	0 - 4
Intramuscular/subcutaneous injections	1.97 (1.89)	1 – 9	1.77 (1.57)	1 – 7	1.86 (1.81)	1 - 10
Intravenous starts	2.20 (2.21)	0 – 10	2.39 (2.26)	0 – 12	2.40 (2.50)	0 - 11
Tape removal	2.81 (1.39)	0 – 6	2.55 (1.43)	1 – 6	2.66 (1.48)	1 - 6
Nasogastric tube insertion	5.25 (4.01)	1 – 16	5.34 (4.03)	1 – 17	5.21 (4.12)	1 - 19
Suctioning through endotracheal tube	9.69 (10.72)	0 – 60	10.00 (11.07)	0 – 60	9.97 (8.75)	0 - 34
Surfactant administration	1.25 (0.45)	0 – 2	1.25 (0.62)	1 – 3	1.31 (0.63)	1 - 3
Intubation	2.59 (3.12)	1 – 17	2.21 (1.37)	1 – 6	2.72 (2.30)	1 – 12
Lumbar punctures	1.17 (0.41)	0 – 2	1.10 (0.20)	0 – 1	1.13 (0.35)	0 – 2
Umbilical Line placement	1.58 (0.51)	0 – 2	1.92 (0.49)	1 – 3	2.21 (0.70)	1 – 4

Research Questions

Primary Research Question

The primary goal of the study was to determine the most efficacious method of relieving pain for neonates having a heel lance. As the duration of the heel lance varied due to the amount of blood required and the ease of attaining the sample, the amount of data available for analyses for each neonate was inconsistent. All study neonates (100%) had a PIPP score computed at 30 seconds after the lance phase. Ninety two percent of the neonates had a second PIPP score computed at 1 minute after the lance phase ($n = 176$). Results will be presented for PIPP scores at 30 and 60 seconds following the heel lance.

There were significant overall differences in PIPP scores at 30 seconds ($F = 8.23$, $p < 0.001$) and 60 ($F = 8.49$, $p < 0.001$) seconds after the heel lance, favoring the sucrose and NNS groups. The mean PIPP scores among intervention groups were consistently higher at 60 seconds (squeeze phase) compared to those at 30 seconds (lance and squeeze phase). The comparisons between intervention groups at 30 and 60 seconds following the heel lance are summarized in Tables 9 and 10.

The mean PIPP scores at 30 seconds were highest in the water and NNS group, and lowest in the sucrose and NNS group. Post hoc Tukey tests at 30 seconds indicated that neonates who received sucrose and NNS had significantly lower PIPP scores compared to neonates who received sucrose alone ($p = 0.007$) or water and NNS ($p < 0.001$). No significant differences in PIPP scores between sucrose alone or water and NNS groups were found ($p = 0.72$).

Table 9

Between-Group Comparisons of PIPP Scores at 30 seconds

ANOVA	Sum of Squares	Degrees of freedom	Mean square	<u>F</u>	p
Between Group	147.18	2	73.59	8.23	< 0.001
Within Group	1673.03	187	8.95		
Total	1820.21	189			

Table 10

Between-Group Comparisons of PIPP Scores at 60 seconds

ANOVA	Sum of Squares	Degrees of freedom	Mean square	<u>F</u>	p
Between Group	219.83	2	109.92	8.49	< 0.001
Within Group	2241.16	173	12.96		
Total	2460.99	175			

The mean PIPP scores at 60 seconds were also highest in the water and NNS group and lowest in the sucrose and NNS group. Post hoc Tukey tests at 60 seconds also indicated that neonates who received sucrose and NNS had significantly lower PIPP scores than neonates who received sucrose alone ($p = 0.005$) or water and NNS ($p = 0.007$). No significant differences in PIPP scores between sucrose alone or water and NNS groups were found ($p = 0.91$). Table 11 summarizes the PIPP scores by intervention groups and the results of post hoc Tukey tests of PIPP scores at 30 and 60 seconds.

Table 11

Results of Post hoc Tukey Tests of PIPP Scores at 30 Seconds and 60 Seconds

PIPP Score (seconds)	Sucrose and NNS Mean (SD) (n)	Sucrose Mean (SD) (n)	Water and NNS Mean (SD) (n)
30	8.16 (3.24) (64)	9.77 (3.04) (62)	10.19 (2.67) (64)
	P = 0.007		P = 0.72
	P < 0.001		
60	8.78 (4.03) (60)	11.20 (3.25) (57)	11.20 (3.47) (59)
	P = 0.005		P = 0.91
	P = 0.007		

Secondary Research Question

The secondary research question was to determine the nature and incidence of adverse effects of sucrose and NNS, sucrose alone or water and NNS. Frequencies of adverse events by phase of the heel lance procedure were computed. Six adverse events occurred during the study period (3%). Neonates were assessed prior to, during and 5 minutes after the painful intervention. Adverse events included choking, coughing or vomiting following the administration of sucrose ($n = 1$), and sustained oxygen desaturation $< 80\%$ for > 15 seconds following the administration of sucrose ($n = 5$).

Three neonates in the sucrose alone group desaturated during the study period but the events resolved spontaneously and no medical or nursing interventions were required. Two neonates in the water and NNS group desaturated during the study period and one neonate choked on the pacifier. No adverse events occurred with neonates randomized to the sucrose and NNS group.

Exploratory Questions

The first exploratory question was posed to determine the influence of gestational age on the safety and efficacy of sucrose and NNS. Neonates were stratified by gestational age to control for the effect of gestational age on the primary outcome. There were 63 neonates in the least mature gestational age stratum (neonates born between 27 and 31 6/7 weeks gestation), 63 neonates in the middle gestational age stratum (neonates born between 32 and 35 6/7 weeks gestation) and 64 neonates in the most mature gestational age stratum (neonates born ≥ 36 weeks gestation).

Differences were found among gestational age strata with respect to delivery type, analgesics during labour, birthweight, gender, Apgar scores, SNAP: PE scores, age at session and multiple births. Neonates, in order of ascending strata, were of greater birth weight and

more mature with significantly lower SNAP: PE scores ($F = 34.88$, $p < 0.001$) and higher Apgar scores at 1 ($F = 11.70$, $p < 0.001$) and 5 minutes ($F = 5.34$, $p = 0.05$). Differences among age strata were also seen in delivery type. Compared to the most mature neonates, the least mature neonates were more likely to have been delivered by Caesarean section with spinal/epidural analgesia ($F = 15.60$, $p < 0.001$). There were slightly more Caesarean births in the middle gestational age stratum, but the differences were not significant. The differences in delivery type may be attributed to the increased use of surgical intervention to manage acute or high-risk preterm births.

Other differences among gestational age strata were noted in the number of multiple births and proportion of male neonates. There were significantly more multiple births ($F = 28.20$, $p < 0.001$) and male neonates ($F = 3.87$, $p = 0.02$) in the least mature age stratum compared to the most mature age stratum. Since twin preterm births are more prevalent at lower gestational ages, it is reasonable to find more twins or higher-order multiples in the least mature age stratum. No significant differences in the number of multiple births or male neonates between the two more mature gestational age strata were found.

Comparison of neonates in the least and most mature strata also revealed a significantly shorter duration of time between the last painful procedure and the time of the scheduled heel lance in the least mature age stratum. The mean duration (hours) of time between the last painful procedure and the scheduled heel lance was 9.09 (SD = 5.89) hours in most mature neonates and 7.39 (SD = 5.79) hours in the least mature neonates ($F = 22.10$, $p < 0.001$). Neonates in the least mature gestational age stratum had significantly more painful procedures than neonates in the other two strata (all $p < 0.001$). The mean number of painful procedures prior to the heel lance procedure for the least mature neonates was 17.22 (SD = 9.40), while the mean number of painful procedures in the middle and most mature strata was 12.34 (SD = 8.76).

and 7.14 (SD = 6.07) respectively. The mean number of non-invasive procedures as defined by nasogastric tube insertion, suctioning, surfactant administration and umbilical line insertion prior to study intervention was also significantly different between gestational age groups with the least mature neonates experiencing significantly more procedures; 34.40 (SD = 15.90), 32.30 (SD = 14.60) and 19.00 (SD = 0) in the least, middle and most mature neonates, respectively. Table 12 summarizes the frequency of painful procedures by age stratum.

Table 12

Frequency of Painful Procedures Prior to Study Entry by Age Stratum

Procedure	27 – 31 6/7 weeks (n = 63) mean (SD)	32 – 35 6/7 weeks (n = 63) mean (SD)	≥ 36 weeks (n = 64) mean (SD)
Heel lances	6.78 (3.55)	6.08 (3.99)	2.98 (2.52)
Venous sticks	3.03 (2.11)	2.11 (1.56)	1.39 (0.86)
Arterial sticks	0.68 (0.88)	0 (0)	0 (0)
Intramuscular injections	1.46 (0.69)	1.46 (1.10)	2.67 (2.61)
Intravenous starts	3.58 (2.16)	2.81 (2.28)	0.64 (1.31)
Nasogastric tube insertion	6.46 (4.17)	4.47 (3.73)	3.48 (3.18)
Suctioning through ETT	16.87 (11.28)	9.48 (8.75)	3.41 (4.24)
Surfactant administration	1.32 (0.60)	1.13 (0.35)	1.00 (0)
Intubation	2.96 (2.84)	1.83 (1.26)	2.25 (1.58)
Lumbar puncture	2.00 (1.00)	1.25 (0.46)	1.00 (0)
Umbilical line placement	1.96 (0.65)	1.70 (0.48)	2.50 (0.71)

Efficacy of sucrose for neonates born between 27 – 31 6/7 weeks gestation. All

neonates in the least mature gestational age stratum had a PIPP score computed at 30 seconds ($n = 63$) and 95% had a second PIPP score computed at 1 minute after the heel lance ($n = 60$). The overall differences among intervention groups were significant for PIPP scores at 30 ($F = 3.70$, $P = 0.03$) and 60 ($F = 3.70$, $p = 0.03$) seconds, in favor of the sucrose and NNS group. Tables 13 and 14 summarize the comparisons between intervention groups in the least mature gestational age stratum at 30 and 60 seconds.

Table 13

Between-Group Comparisons of PIPP Scores in the Least Mature Gestational Age Stratum at 30 Seconds

ANOVA	Sum of Squares	Degrees of freedom	Mean square	F	p
Between Group	62.77	2	31.38	3.70	0.03
Within Group	508.97	60	8.48		
Total	571.75	62			

Table 14

Between-Group Comparisons of PIPP Scores in the Least Mature Gestational Age Stratum at 60 Seconds

ANOVA	Sum of Squares	Degrees of freedom	Mean square	F	p
Between Group	93.83	2	46.92	3.80	0.03
Within Group	705.02	57	12.37		
Total	798.85	59			

The mean PIPP scores for the least mature gestational age stratum at 30 seconds were highest in the water and NNS group and lowest in the sucrose and NNS group. Post hoc Tukey tests at 30 seconds following the heel lance indicated that sucrose and NNS significantly reduced PIPP scores compared to water and NNS ($p = 0.03$). Sucrose and NNS was not significantly different from sucrose alone ($p = 0.42$). No significant differences between sucrose alone and water and NNS were found ($p = 0.27$).

The mean PIPP scores at 60 seconds were also highest in the water and NNS group and lowest in the sucrose and NNS group. Post hoc Tukey tests at 60 seconds following the heel lance also indicated that sucrose and NNS was significantly better than water and NNS ($p < 0.001$). No significant differences between sucrose and NNS and sucrose alone were found ($p = 0.32$). Similarly, no differences between sucrose alone and water and NNS were found ($p = 0.37$). Table

15 summarizes the PIPP scores by intervention groups and the results of post hoc Tukey tests of PIPP scores at 30 and 60 seconds for the least mature gestational age stratum.

Table 15

Results of Post hoc Tukey Tests of PIPP Scores for the Least Mature Gestational Age Stratum at 30 Seconds and 60 Seconds

PIPP Score (seconds)	Sucrose and NNS Mean (SD) (n)	Sucrose Mean (SD) (n)	Water and NNS Mean (SD) (n)
30	7.26 (2.86) (19)	8.39 (3.09) (23)	9.76(2.84) (21)
	P = 0.42		P = 0.27
	P = 0.03		
60	7.89 (2.83) (18)	9.52 (3.61) (21)	11.00(3.92) (21)
	P = 0.32		P = 0.37
	P < 0.001		

Efficacy of sucrose for neonates born between 32 – 35 6/7 weeks gestation. For neonates in the middle gestational age stratum, 100% had a PIPP score at 30 seconds (n = 63) and 89% had a second PIPP score computed at one minute (n = 56). The overall differences among intervention groups for the first PIPP scores at 30 seconds were significant ($F = 4.79$, $p = 0.01$). Subsequent analyses of PIPP scores at 60 seconds following the heel lance also showed significant differences

among intervention groups ($F = 3.10$, $p = 0.05$) in favor of sucrose and NNS. The comparisons between intervention groups in the middle gestational age stratum at 30 and 60 seconds are summarized in tables 16 and 17.

The mean PIPP scores for the middle gestational age strata at 30 seconds were highest in the sucrose alone group and lowest in the sucrose and NNS group. Post hoc Tukey tests at 30 seconds indicated that sucrose and NNS significantly reduced PIPP scores compared to sucrose alone ($p = 0.01$) but not over water and NNS ($p = 0.13$). There were no differences between sucrose alone and water and NNS ($p = 0.50$).

Table 16

Between-Group Comparisons of PIPP Scores in Middle Gestational Age Stratum at 30 Seconds

ANOVA	Sum of Squares	Degrees of freedom	Mean square	F	p
Between Group	84.71	2	42.35	4.79	0.01
Within Group	535.04	60	8.90		
Total	619.75	62			

Table 17

Between-Group Comparisons of PIPP Scores in Middle Gestational Age Stratum at 60 Seconds

ANOVA	Sum of Squares	Degrees of freedom	Mean square	<u>F</u>	p
Between Group	76.5	2	38.25	3.1	0.05
Within Group	639.05	53	12.06		
Total	715.55	55			

Mean PIPP scores at 60 seconds were also highest in the sucrose alone and lowest in the sucrose and NNS group. Similarly, post hoc analyses at 60 seconds indicated sucrose and NNS significantly reduced PIPP scores more than sucrose alone ($p = 0.04$). No differences were found between sucrose alone and water and NNS ($p = 0.25$). No differences between sucrose and NNS and water and NNS were found ($p = 0.63$). Table 18 summarizes the PIPP scores by intervention groups and the results of post hoc Tukey tests of PIPP scores for the middle gestational age stratum at 30 and 60 seconds.

Table 18

Results of Post hoc Tukey Tests of PIPP Scores for the Middle Gestational Age Stratum at 30 and 60 Seconds

PIPP Score (seconds)	Sucrose and NNS Mean (SD) (n)	Sucrose Mean (SD) (n)	Water and NNS Mean (SD) (n)
30	7.59 (2.89) (22)	10.42 (3.45) (19)	9.36(2.63) (22)
	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> $P = 0.01$ </div> <div style="text-align: center;"> $P = 0.50$ </div> </div> <div style="text-align: center; margin-top: 10px;"> $P = 0.13$ </div>		
60	9.16 (4.32) (21)	12.00 (2.59) (17)	10.16 (3.24) (18)
	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> $P = 0.04$ </div> <div style="text-align: center;"> $P = 0.25$ </div> </div> <div style="text-align: center; margin-top: 10px;"> $P = 0.63$ </div>		

Efficacy of sucrose for neonates born ≥ 36 weeks gestation. For neonates in the most mature gestational age stratum, 100% had one PIPP score at 30 seconds ($n = 64$) and 94% had a second PIPP score at 60 seconds ($n = 60$). The overall differences among intervention groups were significant for the first ($F = 3.20$, $p = 0.04$) and second PIPP score at one minute ($F = 4.77$, $p = 0.01$) favoring the sucrose and NNS group. The comparisons between intervention groups in the most mature gestational age stratum at 30 and 60 seconds are summarized in tables 19 and 20

Table 19

Between-Group Comparisons of PIPP Scores in Most Mature Gestational Age Stratum at 30 Seconds

ANOVA	Sum of Squares	Degrees of freedom	Mean square	<u>F</u>	p
Between Group	47.34	2	23.67	3.20	0.04
Within Group	444.64	61	7.29		
Total	5491.98	63			

Table 20

Between-Group Comparisons of PIPP Scores in Most Mature Gestational Age Stratum at 60 Seconds

ANOVA	Sum of Squares	Degrees of freedom	Mean square	<u>F</u>	p
Between Group	124.60	2	62.30	4.77	0.01
Within Group	745.05	57	13.07		
Total	869.65	59			

The mean PIPP scores for the most mature neonates at 30 seconds were highest in the water and NNS group and lowest in the sucrose and NNS group. Post hoc tests at 30 seconds

indicated that sucrose and NNS significantly reduced PIPP scores compared to water and NNS ($p = 0.04$) but not sucrose alone ($p = 0.26$). No significant differences between sucrose alone and water and NNS were found ($p = 0.67$).

The mean PIPP at 60 seconds were highest in the sucrose alone and lowest in the sucrose and NNS group. Post hoc Tukey tests at 60 seconds following the heel lance indicated that sucrose and NNS was significantly better than water and NNS ($p = 0.02$) and sucrose alone ($p = 0.03$). No differences between sucrose alone and water and NNS were found ($p = 0.98$). Table 21 summarizes the PIPP scores by intervention groups and the results of post hoc Tukey tests of PIPP scores for the most mature gestational age stratum at 30 and 60 seconds.

Table 21

Results of Post hoc Tukey Tests of PIPP Scores for the Most Mature Gestational Age Stratum at 30 and 60 Seconds

PIPP Score (seconds)	Sucrose and NNS Mean (SD) (n)	Sucrose Mean (SD) (n)	Water and NNS Mean (SD) (n)
30	9.43 (3.55) (23)	10.75(2.05) (20)	11.48(2) (21)
	P = 0.26		P = 0.67
	P = 0.04		
60	9.19 (4.64) (22)	12.33(2.7) (19)	12.10(3.08) (19)
	P = 0.03		P = 0.98
	P = 0.02		

Safety of sucrose for each gestational age stratum. There were six adverse events during the study intervention period. No adverse events occurred in the sucrose and NNS group. Of the adverse events, four of them occurred in the least mature gestational age stratum (27 – 31 6/7 weeks). One neonate in the least mature gestational age stratum, who had been randomized to the water and NNS group, choked when the water was placed in his mouth. The neonate stabilized within 10 seconds and the heel lance procedure continued. Three neonates in the least mature gestational age stratum, who had been randomized to the sucrose group, desaturated when sucrose was delivered into their mouths. Each neonate recovered spontaneously and no medical or nursing interventions were required to stabilize the neonates.

One neonate in the middle (32 – 35 6/7 weeks) and one in the most mature age stratum (>36 weeks) desaturated during the study intervention period. Both of these neonates had been randomized to the water and NNS group. Although more adverse events occurred in the least mature gestational age groups, none of the events were considered clinically significant by the attending neonatologist and no interim analysis was performed.

The second exploratory question was posed to examine differences in neonates' individual behavioral (brow bulge, eye squeeze and nasolabial furrow) and physiological (heart rate and oxygen saturation) indicators of pain in the sucrose and NNS, sucrose alone and water and NNS groups (as compared to the composite measure of pain determined by the PIPP) for each phase of the heel lance procedure.

Significant overall differences were found in brow bulge during the warming ($F = 10.33$, $p < 0.001$), lance ($F = 8.96$, $p < 0.001$), squeeze ($F = 14.87$, $p < 0.001$) and return to baseline ($F = 4.63$, $p < 0.01$) phases of the heel lance procedure. Significant differences were also found in eye squeeze during the lance ($F = 7.21$, $p < 0.001$) and squeeze ($F = 7.44$, $p = 0.01$) phases of the

heel lance procedure. Similarly, significant differences in nasolabial furrow were found during the lance ($F = 3.03$, $p = 0.05$) and squeeze ($F = 3.60$, $p = 0.03$) phases. No intervention effects on eye squeeze or nasolabial furrow were found at any other phase of the procedure.

Post hoc analyses using brow bulge, eye squeeze and nasolabial furrow as indicators for pain again indicated that sucrose and NNS significantly reduced the individual behavioral indicators of pain scores over the other two intervention groups (all indicators significant at $p < 0.001$).

When physiological (heart rate and oxygen saturation) indicators were used as indicators of pain, significant differences were found in heart rate during the warming phase ($F = 3.79$, $p = 0.02$). No physiological differences were found among intervention groups during any other phases of the heel lance procedure. Post hoc analyses indicated that neonates who received sucrose and NNS had significantly lower heart rates during the warming phase ($F = 3.79$, $p = 0.02$) compared to sucrose alone or water and NNS. Table 22 summarizes the significant individual behavioral and physiological indicators of pain for each phase of the heel lance procedure.

Table 22

Significant Individual Indicators of Pain by Phase of the Heel Lance Procedure

Indicators	Phases				
	Baseline	Warming	Lance	Squeeze	Return to baseline
Brow bulge		X	X	X	
Nasolabial furrow			X	X	
Eye squeeze			X	X	
Heart rate		X			
Oxygen saturation					

Note. The X represents significant differences among intervention groups, favoring the sucrose and NNS group, at $p < 0.05$

Secondary Analysis

A hierarchical multiple regression analysis was used to determine which variables contributed to the variance in the major outcome pain, as assessed by PIPP scores. Correlation coefficients of continuous variables at the time of randomization were performed and only one of the two highly correlated variables was entered into the regression model (see Appendix F for correlation coefficients). Only variables existing at the time of randomization were entered into

the analyses. Continuous variables such as severity of illness, Apgar score, number of painful procedures were entered into the model depending on their predicted influence on the dependent variable, PIPP score. Variables with the most likelihood of influence were entered first.

Variables with the least possibility of intervention were entered last. Dummy variables were used to indicate categories of gender, type of delivery and intervention groups. Gestational age and behavioral state were not entered into the regression model because they are included in the PIPP as contextual indicators.

In the model, intervention group was entered first as it had the most potential for contributing to the variance in PIPP scores. Neonatal characteristics of number of painful procedures, severity of illness, type of delivery (forceps, caesarean, vacuum) and gender were entered last. Intervention group explained 9 % of the variance and gender explained 3 % of the variance. All other variables were deleted from the final model as they did not explain anything further in the presence of gender and intervention group.

Intervention group and gender were the only significant variables to explain some of the variance in PIPP scores, contributing to 12 % in the final model. There were associations between gender and PIPP scores, with male neonates having significantly higher PIPP scores than female neonates. The mean PIPP score for males was 9.73 (SD = 2.92) and 9.01 (SD = 3.25) for females, however, the differences were small and not clinically significant. The final model is described in Table 23.

Table 23

Hierarchical Regression Analysis for PIPP scores

Step	Variable Added	$\underline{R}$	$\underline{R}^2$	Change in $\underline{R}^2$	$\underline{F}$	p	Degree of freedom
1.	Intervention group	0.28	0.09	—	15.89	0.001	2
2.	Gender	0.32	0.12	0.03	7.71	0.001	1

Summary of Results

A combination of sucrose and NNS is the most efficacious intervention for relieving procedural pain associated with heel lances in preterm and term neonates. Pain was measured by a valid composite pain measure, using the PIPP (Stevens et al., 1996). PIPP scores in the sucrose and NNS group were significantly lower at 30 and 60 seconds following the heel lance compared to sucrose alone or water and NNS. These data indicate that a combination of sucrose and NNS is more efficacious than the other methods of sucrose administration, and the efficacy of sucrose and NNS lasts 60 seconds after the painful procedure.

Very few adverse events ($n = 6$) occurred during the study period and each of the events resolved spontaneously. No adverse events occurred in the sucrose and NNS group.

Sucrose and NNS reduced pain responses in each gestational age stratum at 30 and 60 seconds following the heel lance. PIPP scores generally increased over time but remained lower in the sucrose and NNS group compared to the other two interventions. In addition, there was a trend towards a greater difference in PIPP scores between intervention groups at 60 seconds

compared to 30 seconds. Adverse events occurred more frequently in the least mature gestational ages. However, the adverse events were minor in nature and did not require medical or nursing intervention.

Individual behavioral and physiological indicators of pain were significantly different among intervention groups, with less individual pain responses in the sucrose and NNS group compared to sucrose alone or water and NNS. Intervention group and gender explained 12 % of the variance in PIPP scores. Other variables not measured in the present study such as severity of illness, environmental light or noise may explain the remainder of the variance.

All results related to the research questions are summarized in Table 24

Table 24

Summary of Research Results

Research Question	Statistical Value	Significance
1. Efficacy of Sucrose and NNS		
PIPP at 30 seconds	$\underline{F} = 8.23$	$p < 0.001$
PIPP at 60 seconds	$\underline{F} = 8.49$	$p < 0.001$
2. Safety of Sucrose and NNS		
Frequency of adverse events	6	not applicable
3. Influence of Gestational age on Efficacy of Sucrose and NNS		
27 – 31 $\frac{6}{7}$ weeks		
PIPP at 30 seconds	$\underline{F} = 3.70$	$p = 0.03$
PIPP at 60 seconds	$\underline{F} = 3.80$	$p = 0.03$
32 – 35 $\frac{6}{7}$ weeks		
PIPP at 30 seconds	$\underline{F} = 4.79$	$p = 0.01$
PIPP at 60 seconds	$\underline{F} = 3.10$	$p = 0.05$
≥ 36 weeks		
PIPP at 30 seconds	$\underline{F} = 3.20$	$p = 0.04$
PIPP at 60 seconds	$\underline{F} = 4.77$	$p = 0.01$

Chapter V

DISCUSSION

The purpose of this study was to compare the efficacy and safety of three methods of eliminating procedural pain in preterm and term neonates. The ultimate goal of this study was to contribute to the body of knowledge on the management of procedural pain in neonates and provide evidence for clinical guidelines and evidenced based practice and research.

This chapter is divided into four sections. In the first section, the strengths and limitations of this study will be considered. The second section includes a discussion of the clinical importance of alleviating pain in neonates. The third section includes the three research questions related to procedural pain: (a) the most efficacious method of sucrose administration, (b) the safety of sucrose and (c) the exploration of the influence of gestational age on the efficacy and safety of sucrose, and the exploration of individual behavioral and physiological indicators of pain across the heel lance procedure. As this study identified a significant reduction in mean pain scores in preterm and term neonates following the administration of 0.5ml 24% sucrose with a pacifier, relevant research findings will be re-examined in light of the new evidence. In the fourth and final section, results of the secondary analysis including a regression model will be discussed.

Strengths and Limitations of the Study

Several methodological considerations must be addressed in evaluating the results of this study. Strengths and limitations will be discussed in relation to the study design, sample size, research site and measurement of outcomes (instrumentation).

Design

A major strength of this study was the randomized control trial design. The design included stringent recruitment, randomization, data management and analyses, had a low dropout rate, a well-validated method of determining outcomes, low data-entry error rate and a standardized heel lance procedure. A randomized controlled trial was the most appropriate design to answer the primary research question regarding the most efficacious method of sucrose administration. In this design, characteristics of the subjects included were narrowly defined, randomization was centralized and concealed from the investigator, participants were assigned using a method of centrally controlled randomization to an intervention group (the independent variable) that was manipulated and the dependent variable (pain) was operationalized and measured in a consistent manner using a validated infant pain measure. In addition, all neonates, for whom data were available, were analyzed using the principle of intention to treat. Data were considered missing only if the physiological and/or behavioral data to compute PIPP scores were unavailable due to equipment or observational failure. Otherwise, all neonates who were randomized were included in the analyses.

Characteristics of Subjects. Inclusion criteria were clearly and narrowly defined to provide a reasonably homogenous group for answering the primary research question. Neonates were excluded from the study if medical conditions, diagnoses or treatments interfered with their ability to respond to procedural pain. Similarly, neonates whose parents could not provide consent due to language barriers were not included in the study. The sample was recruited from all eligible neonates.

Randomization was used to assign eligible neonates to one of three intervention groups. Central randomization was performed by a research pharmacist according to an established randomization table for each gestational age stratum to avoid selection bias. Although blinding

of the intervention was only possible for two intervention groups, physiological data collected from a computerized SATMASTER program (EMG, Los Angeles, CA), and behavioral data coded by a facial coder who was blinded to the purpose of the study, improved the internal validity of the results. Internal validity was further strengthened by standardizing the heel lance procedure, the minimum amount of blood required for the test (0.2ml) and by having a single individual perform 95% of the heel lances. No control for the use of pacifiers or frequency of painful procedures outside the study period were made for the study as this practice was not considered ethical.

Prognostic stratification for gestational age was used to control for the effects of maturity at birth on the primary outcome, pain. Although other variables may have influenced PIPP scores, sufficient knowledge of neonates' pain responses based on developing neuroanatomy exist, and stratification for gestational age was a biologically plausible variable that could affect pain responses. However, the sampling method resulted in many neonates, who were eligible for recruitment, not being approached for the study. The resultant delay in recruitment and effect of different time periods during which the study occurred, may have somewhat threatened the ability to generalize the findings. To strengthen the representativeness of the sample, and minimize the interaction of time and treatment (Burns & Grove, 1987), all study participants ($n = 190$) were compared with the hospital's 1999 perinatal database that contains data for all live births in the hospital where the study took place ($n = 3679$). However, since neonates who were in the present study comprised 5% of the study hospital's perinatal database, comparisons between groups must be made with caution.

Comparisons between study participants and refusers ($n = 7$) and losses to follow-up ($n = 12$) were made. No differences between the research sample and hospital's 1999 database, and the refusers or losses to follow-up were found. Although there were limitations with the

sampling technique, data from the hospital's 1999 perinatal database and data from the refusers suggest that the demographic characteristics of study neonates were similar to the neonates born live at this institution during the same year.

At randomization, the three intervention groups were comparable in terms of gestational age, birth weight, age (in days) at enrolment, SNAP scores, time since last feed, Apgar scores and time since last painful procedure.

Sample Size

Another strength of this study is that the sample size allowed for sufficient power to answer the primary research question. Existing studies examining the efficacy of sucrose included small sample sizes that were unable to detect significant differences in composite pain responses. A sample size of 186 was required to answer the primary research question. Therefore, 202 neonates were recruited to account for possible losses. Data for 12 neonates were considered missing because of technical difficulties, leaving a sample of 190 for data analyses. The study was not powered to detect the effects of gestational age on efficacy of sucrose as this was beyond the time and financial scope of the researcher within the context of the PhD thesis. However, analyses from the exploratory question will be used to generate hypotheses for future research.

Site

The present study was carried out in a standard NICU setting with no manipulation of environmental factors such as light, noise and level of activity. The effects of these factors were not taken into account in the analyses. Further analyses could address the effects of environmental factors on PIPP scores. The heel lance procedure was similar to standard NICU practice, but for research purposes, the phases of the heel lance were differentiated. The use of the principal investigator to perform the vast majority of the heel lances for the study, and the

standardization of the heel lance procedure minimized technician effects and increased the internal validity of the study.

The use of one research site insured tighter control of the potential sources of bias (i.e. technician effect, site differences). However, a single site research study may have resulted in longer recruitment times, history-treatment interactions and populations who may differ from the target population. The investigator was careful to recruit all eligible neonates as quickly as possible (1998/05/21 to 1999/09/23), however, a limitation of a single site is that the results might not be generalizable to all neonates in other NICUs.

Measurement of Outcomes (Instrumentation)

A strength of the present study was the use of reliable and valid outcome measures. The dependent variable, pain, was measured using the PIPP. The “gold standard” for pain is self-report, however, since neonates cannot self-report, their pain is inferred from behavioral and physiological indicators (Anand & Craig, 1996). Although this measure is not consistent with a self-report “gold standard”, it is the best available, as the PIPP is the most validated measure of procedural pain for preterm and term neonates. The PIPP has established reliability and validity for procedural pain for preterm and term neonates ($\alpha = 0.89 - 0.91$). For the present study, intra-rater reliability was performed by an experienced coder who did regular reliability and validity checks after approximately 25 neonates were randomized. The intra-rater reliability was high ($\alpha = 0.93$).

To assure accuracy with physiological data (that compute the PIPP), the SATMASTER program (EMG, Los Angeles, CA) was calibrated with the neonate’s cardiac monitor prior to each heel lance procedure. Discrepancies between the SATMASTER program (EMG, Los Angeles, CA) and the cardiac monitor resulted in the need for manual data collection. The low rate of having to revert to collecting manual data ($n = 8$) further increased the internal validity of

the study. All data were verified for completeness and double entered into a database. There was a very low error rate in data entry (less than 1%).

The Clinical Importance of Alleviating Pain in Neonates

The immediate physiological responses to pain may be protective at times of acute stress. The synthesis and secretion of glucocorticoids to mobilize fat and protein, and increase heart rate and blood pressure enables individuals to maintain autonomic, endocrine and immunological equilibrium (Plotsky et al., 2000). However, the long-term effects of repeated or un-managed pain may result in a depletion of energy stores that contribute to increased mortality and morbidity. Neonates are capable of detecting pain at the peripheral nervous system and transmitting nociceptive impulses to the CNS. However unlike adults, neonates cannot self-report pain. Neonates' physiological and behavioral responses to pain are often unpredictable or un-sustained over time, especially preterm or acutely ill neonates. Therefore, neonates are at greater risk for the long-term consequences of repeated pain when compared to adults or less acutely ill preterm and term neonates. The clinical importance of alleviating pain in neonates is not only to decrease or eliminate the immediate pain responses that contribute to catabolic states, but to improve the potential long-term neurobehavioral outcomes of neonates that experience hundreds of painful procedures during the first few weeks of life.

A growing body of research evidence indicates that sucrose reduces pain responses in preterm and term neonates. In the present study, a single dose of 0.5ml of 24% sucrose administered onto the anterior portion of the tongue followed by the insertion of a pacifier significantly reduced pain, as assessed using a validated composite measure, for all gestational ages compared to sucrose alone or sterile water with a pacifier. The PIPP score is computed by calculating the differences between physiological and behavioral indicators from baseline (no pain) to painful event. A score of less than 6 is considered by clinical experts to reflect minimal

pain and a score of greater than 12 indicates moderate to severe pain (Stevens et al., 1996). Ideally, a pain relieving intervention should reduce PIPP scores to 0, reflecting the elimination of pain. However, the interventions used in the current study failed to eliminate pain completely, with mean PIPP scores for each intervention group averaging a score of greater than 6. Although pain responses were statistically significant favoring sucrose and NNS, determining clinical significance of pain relief in neonates is difficult. While statistical significance refers to whether or not observed differences are true or occurred by chance, clinical significance relates to the importance of the findings to the clinical population (Lefort, 1993; Powell, Kelly & Williams, 2001). There is no universal agreement on the definition of clinical significance; it is best described as the meaningfulness of an outcome to a given individual. The most accurate estimate of clinical significance is obtained by verbal report from the individual receiving the intervention. When self-report is not possible, calculation of (a) the proportion of subjects who improved with the intervention, had no change or deteriorated as a result of the intervention, or (b) the percentage of change as a result of the intervention within the same individual, can be computed (Lefort, 1993). These data are often more helpful to the individual than reporting means or standard deviations for a given analysis.

Due to neonates' inability to communicate individual changes as a result of interventions, the present study can only determine clinical significance by inferring that changes between intervention groups represent differences in degree of pain relief, which is clinically desirable to provide comfort to neonates. A strength of the present study was the a priori identification of clinical significance as 20% (or 2-point difference in PIPP scores) representing the difference between mild-to-moderate or moderate-to-severe pain, which in those capable of self-report would be considered clinically important. Kelly (1998) and Todd et al. (1996) indicate that the minimally clinically significant difference in pain scores in adults is

between 10 and 13%. Powel et al. (2001) reported similar results with children aged 8 to 15. Although these results did not include preterm and term neonates, a reduction of 20% in pain scores is considered to be clinically significant.

Sucrose and NNS was the most efficacious method of pain relief for heel lances at 30 and 60 seconds. The pattern of reduced pain responses over time, favouring the sucrose and NNS group, suggests different degrees of pain between intervention groups. Although determination of clinical significance is not possible with non-verbal neonates, a 2-point difference in PIPP scores, which is similar to a decrease from severe-to-moderate or moderate-to-mild pain in those capable of self-report, could be considered clinically significant. In light of neonates' inability to verbally communicate severity of pain, parallels between adults' self-reports are the best available methods to determine clinical significance. Future studies examining parents' and caregivers' a priori perception of clinically significant reduction in PIPP scores are required.

Discussion of Research Questions

Efficacy of Sucrose and NNS

Sucrose and NNS significantly reduced pain scores for heel lances in preterm and term neonates. These results are generally consistent with comparative studies where differences in pain responses between term (Abad et al., 1993; Gormally, 1996; Haouari, 1995; Ramenghi et al., 1996b; Rushforth & Levene, 1993) and preterm (Bucher, 1995; Johnston et al., 1999; Ramenghi et al., 1996; Stevens et al., 1999) neonates who received sucrose or water for pain associated with heel lances have been observed. Because of the variability of interventions and research methods of studies included in the systematic reviews (Stevens et al., 1997; Stevens & Ohlsson, 1998), the optimal dose, method of sucrose administration and pain outcomes to provide clinical practice guidelines were undetermined. This investigator did not find any

studies that have examined the combined or individual effects of sucrose with a wide range of neonates of varying gestational ages (27 – 42 weeks). Therefore, results from the current study will be examined in light of similarities and differences with existing research studies and the meta-analyses.

Comparison of Present Study with Other Studies using a Validated Infant Pain Measure

The sample size for the present study was based on a previous study using the PIPP for procedural pain in preterm neonates (Stevens et al., 1999). Although PIPP scores in both studies were higher in the water and NNS group compared to the sucrose and NNS group (indicating greater pain), there were differences in mean PIPP scores between the studies, with the present study reporting overall higher PIPP scores. These differences are probably related to the disproportionate number of preterm neonates between Stevens et al. ($n = 122$) and the present study ($n = 63$).

In the present study, the mean PIPP scores were 8.16 ($SD = 3.24$) in the sucrose and NNS group and 10.19 ($SD = 2.67$) in the water and NNS group. Stevens et al. (1999) reported mean PIPP scores for neonates born between 27 and 31 weeks gestation for sucrose and NNS and water and NNS as 7.87 ($SD = 3.35$) and 8.44 ($SD = 3.55$) respectively. PIPP scores are computed by calculating changes from baseline physiological and behavioral indicators. As previously discussed, preterm neonates lack sufficient inhibitory mechanisms as well as immature regulation of the HPA axis, which contribute to less predictable and more variable pain responses (Craig et al., 1993; Grunau et al., 2000; Johnston et al., 1993; Walden, 1997). Similarly, the behavioral pain indicators are also less visible and sustainable in preterm neonates (Grunau et al., 2000; Walden, 1997). Although the musculature of the upper face is developed early in gestation, motor control of small muscles around the mouth is more immature. These developmental differences in preterm neonates may result in less visible facial activity

following painful stimuli (Rinn, 1984; Stratton, 1982). Craig et al (1993) and Johnston et al (1993) reported that facial actions in response to painful stimuli are present in preterm neonates but to a lesser extent than term neonates. These data supported that neonates born at younger gestational ages have less vigorous responses. Consequently, as a result of immature physiological stability and developmental behavioral differences between preterm and term neonates, it is not surprising to find lower PIPP scores for preterm neonates, as reported by Stevens et al (1999).

The effects of repeated pain may also explain the lower PIPP scores in the present study compared to Stevens et al. (1999). Data on long-term consequences of pain indicate that repeated pain may contribute to peripheral sensitization where NMDA receptors become hypersensitive. The resultant state of hyperalgesia contributes to increased response to painful and non-painful stimuli and inability to differentiate between varying intensities of stimuli (Melzack & Wall, 1996). The mean number of painful procedures in the present study was 17.22 (SD = 9.4) compared to 122.00 (11.7) in Stevens et al. (1999). However, these differences were likely due to the neonates' postnatal ages, as neonates in the present study were younger (in postnatal days) at the time of the painful procedure (mean age of 3.23 (SD = 1.95) compared to 8.30 (SD = 0.61) in Stevens et al. (1999) study. Johnston and Stevens (1996) reported that the number of painful procedures explained most of the variance in facial actions following a heel lance. Neonates who had experienced the most painful procedures in the NICU demonstrated less facial actions. Similarly, Grunau et al. (1994b) reported that neonates who experienced many painful procedures during their stay in a NICU were reported by their mothers as less sensitive to pain than their healthy term counterparts. Therefore, it is not unexpected that neonates in the current study, who were younger in post-natal age and had

received fewer painful procedures prior to the heel lance, would have lower PIPP scores than those reported by Stevens et al. (1999).

When PIPP scores of only the preterm neonates (27 – 31 5/7 weeks) in the present study were compared to those reported by Stevens et al. (1999), the results were more consistent in the sucrose and NNS groups, 7.26 (SD = 2.86) compared to 7.87 (SD = 3.35) but not in the water and NNS groups with mean PIPP scores of 9.76 (SD = 2.84) compared to 8.44 (SD = 3.55). Although the trend towards higher PIPP scores in the water and NNS were consistent between studies, the higher PIPP scores in the present study may be a reflection of inadequate sample size ($n = 63$) to detect differences between gestational age strata.

Johnston et al. (1999) reported lower PIPP scores during heel lances in preterm neonates born between 25 and 34 weeks gestation who received triple doses (0.15ml) of 24% sucrose compared to single doses of 24% sucrose (0.05ml) or sterile water. No significant differences between single doses of sucrose and water were found ($F = 3.46$, $p = 0.07$). The mean difference in PIPP scores between the triple doses of sucrose and sterile water was 3-points on the PIPP measure. The present study detected a 2-point difference in PIPP scores between sucrose and NNS and water and NNS. The larger difference in PIPP scores between Johnston et al.'s study (1999) and the present study may be explained by the lack of a control group (sterile water) in the present study. Due to the known findings from Johnston et al.'s study (1999), and the ethical issues already discussed in this thesis, the use of a control group (sterile water) was considered unethical. Therefore, the inclusion of NNS in the present study, which unlike sterile water is a pain relieving intervention, may explain the smaller difference in PIPP scores between the two treatment groups.

In the present study, PIPP scores were significantly lower in the sucrose and NNS group compared to sucrose alone or water and NNS. These findings are consistent with those reported

by Blass and Watt (1999) and Carbajal et al. (1999) and demonstrate that neonates have the capacity to respond to painful stimuli shortly after birth. Although these studies support the findings of the current study, only healthy term neonates were examined. Blass and Watt (1999) reported that NNS is efficacious when the suck rate of term neonates exceeds a threshold of 32 sucks/min. However, for preterm neonates who have insufficient sucking reflexes until approximately 32 weeks gestation, the rate of sucking to achieve pain relief is not possible. Data from the present study also suggest that water and NNS for preterm and term neonates is less efficacious than sucrose and NNS.

Carbajal et al. (1999) reported that sucrose and NNS significantly lowered pain scores associated with venepunctures compared to sucrose alone or water alone (all results significant at $p < 0.01$). No significant differences between sucrose and NNS and water and NNS were found. Unlike the present study that detected significant differences between groups, the non-validated, unidimensional (behavioral) measure of pain may have contributed to failure to detect significant differences between sucrose and NNS and water and NNS.

Pain is thought to be a multidimensional phenomenon including sensory and emotional components (IASP, 1979) that is best described by multiple measures including self-report, physiological or behavioral indicators. Due to neonates' inability to provide self-report, assessment and measurement of their physiological and behavioral indicators should be viewed as proxies for self-report (Anand & Craig, 1996). Carbajal et al. (1999) did not use a composite measure of pain to assess pain, which may explain the differences in study outcomes. Although Blass and Watt (1999) included a multidimensional approach to assessing pain (cry, facial activity and heart rate), the inclusion of cry may have threatened the validity of the results because cry is not a reliable indicator of pain in neonates who are too immature or ill. Stevens et al. (1994) found that up to 50% of neonates do not cry in response to painful procedures.

Studies (Lester, 1984; Lester & Zeskind, 1979) have suggested that the presence or absence of cry provides information about the neonate's biological integrity and not necessarily information about pain perception in high-risk infants. Failure to recognize the difference between inability to cry, due to illness, medical equipment or severe pain, and absence of cry due to absence of pain may threaten the interpretation of the results.

The present study used very small doses of sucrose based on the physiological and developmental capability of preterm neonates to tolerate oral solutions. Despite the small dose, significant differences across age groups were found. These findings are similar to Stevens et al. (1999) who reported a trend towards significant reductions in composite pain scores with a pacifier dipped in 24% sucrose compared to a pacifier dipped in sterile water ($F = 3.62$, $p = 0.059$). The differences between this study and the present study may be explained by the small dose of sucrose used. Although the mechanisms of sucrose remain unclear, animal data suggest that sweet tastes must be detected on the anterior portion of the tongue for opioid mediation to occur. It is argued that the dose of 24% sucrose dipped on a pacifier may have been inconsistent and insufficient for the taste receptors to be stimulated and larger doses would have achieved significant differences between groups. In contrast, Johnston et al (1999) reported significant reductions in composite pain scores with very small doses (0.05 – 0.15ml) of 24% sucrose compared to sterile water, thereby suggesting opioid mediation had occurred. These findings are difficult to compare to the present study in light of the different study designs and small sample size ($n = 48$) used by Johnston et al. (1999). It is not clear whether small doses of sucrose are efficacious only when compared to sterile water or whether small doses of sucrose and NNS can achieve pain relief. Because of the differences in design, comparisons between these two studies are not possible.

In the present study, the mean PIPP scores at 60 seconds were lowest in the sucrose and NNS group and highest in the water and NNS group. Although the trend towards lower PIPP scores in the sucrose and NNS group at 60 seconds was similar to those reported at 30 seconds, the scores were generally higher over time. These findings are consistent with Porter et al. (1999). As procedures become more invasive, as measured by duration of procedure and/or intensity of pain, the magnitude of physiological and behavioral responses increase. Porter et al. (1999) also reported that the magnitude of physiological and behavioral change is not affected by gestational age; neonates of all gestational ages can differentiate procedural invasiveness. Similarly, neonates of all gestational ages demonstrate increased magnitude in response to increased duration (in seconds to minutes) of the procedure. These results are consistent with the present study. Neonates in each gestational age stratum had increased PIPP scores at 60 seconds, suggesting that the prolonged squeeze phase is more invasive than the lance phase.

In the present study, the differences in PIPP scores between 30 and 60 seconds were smallest in the sucrose and NNS group. The smaller differences in PIPP scores over time, in the sucrose and NNS group compared to the other two intervention groups, suggest that efficacy of sucrose and NNS persists and therefore is more effective over time.

Safety of Sucrose

Prior to this trial, the combination of sucrose and NNS was thought to be safe compared to sucrose alone or water and NNS. However, no researchers had really examined the safety of this intervention except for one study with a limited sample and methodological rigour previously discussed (Willis et al., 1977). In a pilot study (Stevens et al., 2000b) using consistent use of sucrose and NNS for all painful procedures, fewer adverse events occurred in the sucrose and NNS group compared to the swaddling/positioning or sterile water and NNS groups. In the present study, very few adverse events ($n = 6$) occurred, and although no adverse

events occurred in the sucrose and NNS group, the small numbers preclude any definitive assurance of safety. Further research regarding repeated doses of sucrose and NNS is required.

Despite the attempt to recruit all eligible neonates, neonates in the present study were generally healthy (as measured by SNAP: PE scores) with birth weights that were average for their gestational age. The safety criteria for the present study included events that occurred 5 minutes following the intervention. Although no other studies have examined the incidence or frequency of choking, tachycardia, bradycardia, tachypnea, dsypnea or oxygen desaturation, no data on other adverse events such as hyperglycemia or NEC are available. Since the present study employed a single intervention, these adverse outcomes are unlikely, however, further examination of these events over time are required prior to the use of sucrose and NNS for repeated painful procedures.

Influence of Contextual Factors on Physiological and Behavioral Indicators of Pain within

Study Groups

Influence of Gestational Age on Efficacy of Sucrose

In the present study, the PIPP scores were lowest in the least mature gestational age group (27 – 31 6/7 weeks) and highest in the most mature gestational age group (≥ 36 weeks). The rationale for lower PIPP scores can be explained by the physiological and behavioral immaturity with the least mature age stratum. As neonates mature, the ability to visualize and therefore measure differences in behavioral indicators is easier. Despite differences in PIPP scores at different gestational ages, sucrose and NNS was more effective for reducing PIPP scores at 30 and 60 seconds than sucrose alone or water and NNS. Across gestational age groups, the PIPP scores generally increased over the duration of the intervention suggesting increased invasiveness of the procedure. These findings are well supported in the literature and have been discussed in early sections of this thesis. Allen et al. (1996) reported that efficacy of

sucrose decreases with post-conceptual age (PCA). Healthy term neonates at 2 weeks PCA had significantly less crying time ($F = 5.92, p < 0.05$) when they received sucrose prior to immunization. When the neonates were followed to 18 months corrected age, sucrose was only efficacious if they received one immunization rather than two. A multiple regression analysis with PCA, technician effect, infant condition and time required to perform the immunization were used as predictors for percentage of crying. PCA of the infant at the time of data collection was the only variable that predicted percentage of crying, with younger infants crying significantly longer ($F = 3.36, p < 0.01$). Barr et al. (1994) also reported that the efficacy of sucrose decreases with PCA. Newborn neonates who received sucrose had a 60% reduction in crying time compared to those who received water. These differences were not as dramatic in 6-week old infants. The present study only included neonates within the first 7 days of life, with a mean age at study session (in days) of 3.23 (SD = 1.95). Therefore, efficacy of sucrose based on PCA could not be examined.

The combination of sucrose and NNS was significantly better than water and NNS in both the least and most mature gestational age groups at 30 seconds. No significant differences between sucrose and NNS and sucrose were found. For the least and most mature neonates, the differences in PIPP scores between 30 and 60 seconds were consistently smaller in the sucrose and NNS group compared to the other two intervention groups. These findings are consistent with previous studies suggesting that irrespective of gestational age, it is the taste of sucrose that reduces pain responses. These findings further indicate that efficacy of sucrose and NNS for the least and most mature neonates persists to at least 60 seconds.

Sucrose and NNS was significantly better than sucrose alone in the middle gestational age stratum (32 – 35 6/7 weeks). No significant differences between sucrose and NNS and water and NNS were found. It is not clear why neonates in the middle gestational age stratum

were different on some variables from the most immature and most mature gestational age groups, but the sample size was not powered to detect differences between gestational age strata, and this lack of sufficient power may account for this spurious result. However, the differences in PIPP scores between 30 and 60 seconds following the heel lance were consistently lower in the sucrose and NNS group compared to the other two intervention groups. These findings are consistent across gestational age groups and suggest that efficacy of sucrose and NNS persists to 60 seconds. Further research will need to be conducted to determine the effect of sucrose over time.

Influence of Gestational Age on Safety of Sucrose

In the present study, few adverse events occurred. However, more events were found in the least mature gestational age group ($n = 4$) compared to the middle ($n = 1$) or most mature ($n = 1$) gestational age group. None of the events occurred in the sucrose and NNS group. No studies have examined the nature and incidence of adverse events with the administration of sucrose with different gestational ages; however, the data are consistent with the physiological immaturity of preterm neonates. Due to physiological and developmental differences in preterm neonates, the present study used 50% of the recommended sucrose (0.12g) dose (Stevens et al., 1997). Despite a lower volume given in the present study, the least mature neonates were more likely to desaturate during the procedure than the neonates in the other two gestational age strata. Similarly the least mature neonates were more likely to choke when the pacifier was introduced into their mouth. The immature and disorganized suck reflex prior to 32 weeks gestation may explain the increased frequency of choking with pacifiers in the most immature neonates. Similarly, the inconsistent physiological responses of preterm neonates in conjunction with the increased severity of illness (as measured by SNAP: PE scores) further explain why adverse events are more likely to occur in the most immature neonates.

Despite the increased incidence of adverse events in the least mature age stratum, the nature of the events was considered clinically non-significant by the attending Neonatologist. Future studies examining the nature and incidence of adverse events in relation to repeated doses of sucrose for a wide range of gestational ages is required.

Differences in Pain Indicators in the Intervention Groups for each Phase of the Heel Lance

The behavioral indicators of pain were significantly different among intervention groups with less brow bulge, eye squeeze and nasolabial furrow during the lance and squeeze phases in the sucrose and NNS group. These results are similar to those reported by Johnston et al. (1999) in a study comparing sucrose and sterile water. Facial actions typically observed during painful events were less evident in the group of neonates who received sucrose prior to a heel lance. No other researchers have compared changes in individual indicators of the PIPP in different intervention groups.

Preterm and term neonates' facial actions in response to painful stimuli have been described in many studies (Craig, 1992; Craig et al., 1993; Grunau and Craig, 1987; Johnston et al., 1996; Stevens, 1993; Walden, 1997). Facial activity has been reported as the most consistent response to painful stimuli across studies and different infant (Craig, 1992) and adult (Craig and Patrick, 1985; Patrick, Craig and Prkachin, 1986) populations. In the present study, sucrose and NNS significantly reduced behavioral indicators across gestational age groups.

In the present study, differences in oxygen saturation among intervention groups were found. Neonates who received the combination of sucrose and NNS had 3% less degree of oxygen desaturation during the lance phase compared to the other intervention groups. These findings are consistent with those reported by Porter et al. (1999), where a gradient in response magnitude (desaturation) was observed with mild-moderate and moderate-highly invasive procedures (all p values < 0.01). Similarly, Stevens (1993) reported lower oxygen saturation

during the lance and squeeze phases of a heel lance procedure in preterm neonates 32 – 34 weeks gestational age. Walden (1997) reported, with the exception of neonates at 28 and 30 weeks PCA, significantly lower oxygen saturation during the heel lance phase compared to baseline phase for neonates born between 27 – 32 weeks ($F = 2.71$, $p = 0.007$).

In the present study, significant differences in lowest maximum heart rate during the warming (or non-painful) phase following the administration of sucrose and NNS were found. These findings have not been supported in the literature. Endogenous opioids, mediated by the sweet taste of sucrose, and the production of serotonin induced by sucking activity are hypothesized to reduce heart rates significantly more than either intervention alone. However, further research to test this hypothesis is required. Significant increases in heart rate from baseline to procedural pain have been reported in many studies (refer to Appendix A) and are consistent with the present study. However, in the present study, no differences in maximum heart rate among the three intervention groups were found.

Secondary Analysis

In this study, the PIPP scores were significantly associated with intervention group and gender, which explained 9 and 3% respectively of the variance in PIPP scores. Gestational age and behavioral state were not included in the model because they are included in the PIPP scores. The hypothesis that sucrose and NNS would reduce PIPP scores was supported for the total sample, as well as within each age stratum. Neonates of younger gestational ages had lower PIPP scores compared to older preterm and term neonates and these data can be explained by the physiological and behavioral immaturity. The hypothalamic, pituitary and adrenal response to nociceptive stimuli is less developed in preterm neonates and subsequent responses to nociception are less organized and predictable. Similarly, facial activity in response to painful procedures is less visible in preterm neonates due to immature facial musculature as well as

more technically difficult due to medical equipment such as endotracheal tubes obscuring facial features.

Gender contributed to 3% of the variance in PIPP scores. Although mean PIPP scores were higher in male neonates with mean scores of 9.73 (SD = 2.92) compared to females with mean scores of 9.01 (SD = 3.25), the differences are small and unlikely to be clinically significant. Further examination of gender differences in pain responses in preterm and term neonates may be warranted. Other variables such as SNAP: PE scores, Apgar scores, number of prior painful procedures or time since last painful procedure were not significantly related to pain scores. Although studies have found that these variables affect pain scores, neonates in the present study were healthy with little variability. It is not surprising that similarities in these variables resulted in failure to explain variance in PIPP scores.

Stratification for gestational age was used to control for the effects of age on the primary outcome. Gestational age was thought to be highly correlated with birth weight. Therefore, stratification for gestational age would also control for the effects of the correlated variables on PIPP scores. This hypothesis was supported in the current study and may further explain why birth weight did not contribute to variance in PIPP scores. To test the significance of these variables, future studies examining the individual contribution of each variable are required.

Although the regression model explained only 12% of the variance of PIPP scores with two variables, the goal of the present study was not to predict neonatal pain. Studies with a more heterogeneous sample of neonates will be required in order to examine the influence of other variables and account for the 88% of the variance not explained in the present study.

Chapter VI

IMPLICATIONS FOR THEORY, RESEARCH AND PRACTICE

This study provides a unique contribution to the safety and efficacy of sucrose for preterm and term neonates. Implications of this study will be addressed in three sections. The first section will present implications for clinical practice. The second section addresses the development of the theoretical model in light of the research findings and the final section will offer directions for future research.

Implications for Clinical Practice

Each neonate in this study experienced at least one painful procedure during his/her stay in the NICU, with the majority of neonates experiencing several painful procedures. Nurses are responsible for providing direct care to NICU patients and are most often the individual performing the painful procedures. Although pain management for neonates has improved over the last few decades, many painful procedures such as heel lances continue to be performed on neonates without appropriate analgesia or comfort measures. The sub-optimal management of pain is related to misconceptions/myths of neonates' capacity to detect, transmit and interpret pain as well as concerns about safety of analgesics. Administration of analgesics to neonates requires careful consideration of the pharmacokinetics (movement of drugs in the body over time) and pharmacodynamics (dose-response relationship) of the specific agent (Stevens et al., 2000a). In addition, developmental differences between the metabolic functions of preterm and term neonates' must be considered prior to the administration of analgesics. Due to the frequency of painful events and the concerns over cumulative effects of analgesics, it may not

be safe or feasible to administer analgesics for each heel lance performed in the NICU.

Therefore, alternative approaches that are safe and efficacious are required.

In this study, sucrose and NNS significantly reduced pain scores during a heel lance in preterm and term neonates compared to sucrose alone or water and NNS. Irrespective of gestational age, the intervention reduced pain scores at 30 and 60 seconds after the painful event. Although there were a few adverse events during the study period, they were benign in nature, resolved spontaneously and did not require medical or nursing intervention. In light of the relatively simple, yet efficacious, intervention to manage neonatal pain, changes in pain practice for selective painful procedures could easily be incorporated into standard NICU care.

Sucrose and NNS are readily available in hospital nurseries, inexpensive, easily administered and safe. In addition, the long history of use of sweet solutions and pacifiers for painful procedures further increase the likelihood of acceptance of sucrose and NNS as routine interventions for pain management in the NICU. Given the rapid and enduring effects of sucrose and NNS, they can be given together in advance of minor to moderate procedural pain. Although sucrose and NNS is not efficacious for moderate-severe pain, the combined therapy can be used as an adjunct with pharmacological interventions.

The PIPP is a valid and reliable measure with emerging evidence of its clinical utility (Schiller, Stevens, Sidani, Ballantyne and McNair, 1999). The physiological data that are used to compute PIPP scores are easily obtainable from standard NICU monitoring equipment and recorded in medical and nursing notes. Second-to second physiological data are available from most cardiac monitors and can be printed upon request for analyses. For neonates who do not have a cardiac monitor as part of their routine NICU care, physiological monitoring of heart rate and oxygen saturation could be manually calculated and later analyzed. However, since these

neonates are experiencing a painful procedure, portable cardiac and oxygen saturation monitoring equipment could easily be used.

Gestational age is computed primarily by the obstetrical team (based on mother's last menstrual period or ultrasound data), but can be assessed by neonatal health care providers using the Dubowitz scoring system (Dubowitz, 1970). In any case, knowledge of gestational age is available in the neonate's medical chart and can thus be used to compute PIPP scores. Assessment of behavioral state prior to any intervention is currently performed by NICU team members. Neonates in crying states are typically consoled prior to attempting a painful procedure. Although an attempt to console a distressed neonate is often made to facilitate the operator's attempt to perform the painful procedure rather than reduce the neonate's cumulative pain, awareness of behavioral state can easily be incorporated into standard NICU practice, and used to compute PIPP scores.

Behavioral data are readily available from the faces of most neonates. However, on occasion individual indicators, such as nasolabial furrow, may be difficult to assess due to the presence of endotracheal tubes or other equipment. For these instances, consideration of the total PIPP must be taken in light of the missing data. The individual indicators of the PIPP are available for most neonates in the NICU. Assessment of the 7 indicators at the neonate's bedside is relatively easy and scoring the PIPP involves computing individual indicators. Preliminary evidence of the PIPPs clinical utility suggest that it can be used easily by all members of the health care team to assess the presence of pain during a procedure (Schiller et al., 1999).

Despite the evidence that sucrose and NNS is a safe intervention that reduces procedural pain, changes in pain practices will not occur until NICU staff recognize the (a) existence of neonatal pain, (b) physiological and behavioral indicators of pain and (c) immediate and long-

term consequences of pain. Ongoing pain education to all health care disciplines in the NICU is required. Orientation teaching sessions that include pain assessment and management as well as ongoing inservices to all NICU staff may encourage the commitment to optimal pain management. Forums to challenge existing practices and discuss research evidence related to practice may enable health care providers to express their concerns over patient care issues. Pain management committees that evaluate pain practices and make evidence-based recommendations for change is a first step towards implementing new pain practices.

Since nurses provide most of the direct care to neonates in the NICU, specific opportunities for them to question pain management practices, share personal opinions and offer suggestions to implement changes to current pain management practice is required. Training opportunities for nurses to learn how to use the PIPP will improve pain assessment of all neonates. Implementation of pain management practices that include sucrose and NNS can only occur once nurses' assessment of pain is obtained. Specific NICU guidelines for procedural pain management that are based on the existing guidelines from the American Academy of Pediatrics and the Canadian Paediatric Society (Pediatrics and Child Health, 2000) should be developed in conjunction with medical, nursing, pharmacy and respiratory staff. Guidelines that include the administration of sucrose and NNS for heel lances in preterm and term neonates should be considered and quality indicators measuring competencies and effectiveness of these guidelines are essential. Evaluation of pain management practices can occur through performance appraisals, staff surveys and parental feedback.

Finally, unit-specific mission statements and formal institutional policies on pain management practices that are supported by hospital administrators and unit managers should be initiated. Mission statements that recognize neonatal pain and promote the management of pain should be visible in all patient care areas. Parents must be provided with a copy of the

NICU mission statement in order to promote their involvement in their neonate's care and further encourage them to become advocates for their neonate's pain management. The involvement of parents during painful procedures should also be considered. However, because parents' presence during painful procedures is not common NICU practice, further review and consideration by the health care team is required. Despite the evidence that sucrose and NNS is a safe and efficacious method of pain relief for preterm and term neonates, changes to practice will not occur until pain management becomes a priority to health care providers and parents. As parents and staff become proactive in pain relief practices, changes such as the implementation of sucrose and NNS are more likely to be sustained

Development of the Theoretical Model

The description of preterm and term neonates' responses to painful procedures highlight the multidimensionality of pain. Data from this study and others support the neonate's complex responses to painful procedures that can be reduced with the administration of sucrose and NNS. These data form the basis for a conceptual framework on which to examine the efficacy of sucrose and NNS with other environmental, behavioral or pharmacological interventions. Efficacy trials examining different interventions with a variety of painful procedures could serve as the framework for pain management.

The original conceptual model for this study proposed that pain is not a simple process, but a process that involves transduction, transmission, perception and modulation of nociceptive impulses within a developing CNS. Based on the GCT, an understanding of neuroanatomy and factors that influence pain response, it was hypothesized that sucrose and NNS would be the most efficacious method of sucrose administration for preterm and term neonates. In the proposed framework, (a) the painful stimulus was a heel lance, (b) the pain responses included physiological and behavioral indicators, (c) the contextual factors included gestational age and

behavioral state that influence pain responses and (d) the mechanisms explained the efficacy of the interventions.

Heel lances were chosen as the painful procedure for the present study because they are the most frequently performed painful procedure in NICUs and the physiological and behavioral responses to heel lances have been studied extensively. In addition, the heel lance procedure could easily be standardized by phases and outcome measures could be standardized by the use of valid instruments. The three interventions were based on data to support the efficacy of sucrose alone or in combination with NNS for preterm and term neonates.

The proposed conceptualization of pain responses is congruent with the multidimensional definition of pain. Responses to pain were conceptualized to reflect the neuroanatomical and developmental differences between preterm and term neonates. Based on previous studies indicating the influence of gestational age and behavioral state on pain responses, these contextual variables were included in the present study by using a validated composite pain measure, the PIPP. Other factors that have been shown to influence pain responses, such age at study session, severity of illness or previous painful procedures were included in the conceptual framework, however, they did not appear to modulate pain responses. Gender explained some of the variance in PIPP scores, with male neonates having statistically but not clinically significant higher pain scores. Environmental factors such as light, music and sound, or care-giving factors such as handling or positioning were not included in the present conceptualization and their contribution to pain responses are not known. This conceptualization will be further tested and refined in future research studies that explore the influence of these factors on neonate's pain response. Additional studies to determine the composite pain responses with different painful stimuli and with repeated painful stimuli are required.

Irrespective of gestational age, the combination of sucrose and NNS was the most efficacious method of pain relief. The mechanisms underlying these effects were not evaluated in the present study, however, it could be speculated that sucrose competes with small diameter afferent fibers to “close the gate” and inhibit nociceptive transmission. In addition, it is hypothesized that sucrose mediates an endogenous opioid response that activates the descending inhibitory mechanisms to block nociceptive transmission at the level of the spinal cord. Consistent with the GCT, the combination of NNS provides immediate orotactile stimulation that further competes with small diameter afferent fibers to “close the gate” and inhibit nociception. It is further hypothesized that the transient efficacy of NNS is related to serotonergic synthesis resulting from sucking behaviors. This conceptualization will be further developed in future research studies that explore the mechanisms of sucrose with or without NNS.

In the proposed conceptualization, stratification for gestational age was used to control for the effect of gestational age on the primary pain outcome. The combination of the two interventions was efficacious for neonates of all gestational ages. However, interaction between efficacy of sucrose and NNS and other developmental, environmental or care-giving factors were not evaluated in the present study. Analyses of these factors form the basis for future research.

Directions for Future Research

The goal of this study was to examine the safety and efficacy of sucrose and NNS for painful procedures and how this was influenced by a wide range of gestational ages. Due to ethical issues previously addressed, no attempt was made to address whether the mechanisms of sucrose and NNS were additive or synergistic. Future studies need to address this issue with other pain management strategies that do not preclude neonates from some form of pain relief.

In particular, examination of sucrose and NNS, sucrose alone, water and NNS and water alone with positioning/containing may provide insight into the mechanisms of individual and combined treatments of sucrose and NNS. There are sufficient animal data on sucrose to draw parallels to human neonates; sucrose appears to be mediated through endogenous opioid pathways and the mechanisms underlying efficacy is most likely induced by sweet taste. However, the mechanisms underlying NNS are unclear. Although a few animal studies suggest multiple pathways including contact, vestibular or serotonergic may be involved, there are insufficient data to draw comparisons to human neonates. Further research identifying the role of sucking in relation to serotonin production in animals is required. In addition, research examining possible feedback or interactive mechanisms between sucking and further production of serotonin may explain the rapid but transient analgesic properties of NNS. Data from animal models can then be used to infer mechanisms of NNS in human neonates.

The current study did not include neonates born less than 27 weeks gestation due to limited data on physiological and behavioral responses with extreme preterm neonates. Although the PIPP has beginning construct validity with all gestational ages, further validation of the psychometric properties (i.e. reliability, validity, sensitivity and specificity) of the measure would need to be established before it could be used in clinical practice or research for the most immature neonates. Similarly, this study did not include neonates who were neurologically impaired (as defined by 5 minute Apgar score < 7 or venous/arterial gas with pH < 7.0), had experienced surgery or who were receiving analgesics for other pathological or medical conditions. Other high-risk neonates who were excluded from the current study were those receiving neuromuscular blocking agents that prevented assessment of behavioral indicators. The exclusion of these high-risk neonates highlight the need for future research. Little is known about the physiological and behavioral pain responses of these infants.

Therefore, the development of a reliable and valid measure for assessing high-risk neonates' responses to pain is required. Interventions to manage pain in these high-risk populations can only occur once reliable and valid measures are developed.

Sucrose and NNS reduce individual behavioral indicators associated with pain, specifically brow bulge and eye squeeze. Maximum heart rate and minimum oxygen saturation were also reduced with the administration of sucrose and NNS but the magnitude of these indicators were affected by gestational age with the most immature neonates demonstrating the least physiological changes. The differences in responses are explained in terms of infant development. Neonates of younger gestation are less able to express pain responses through specific facial actions. Moreover, preterm neonates' disorganized inhibitory mechanisms and physiological immaturity to modulate nociceptive impulses contribute to inconsistent pain responses. Future studies that attempt to assess what individual indicators are most predictive of pain responses for varying gestational ages are required.

In this study, sucrose and NNS was not associated with major adverse events. Previous data (Willis et al., 1977) suggest that sucrose contributes to the development of NEC. However, as previously discussed, the methodological flaws in the study preclude any meaningful conclusions. One preliminary study (Stevens et al., 2000b) found fewer adverse events in the sucrose and NNS group compared to the standard group. Although only a few adverse events occurred during this study, the intervention was used for a single painful event. Future research should address adverse events with repeated doses of sucrose and NNS. Preliminary animal data suggest that long-term or repeated doses of sweet tasting solutions may alter efficacy to subsequent opioid administration for painful procedures. Therefore, it is essential to determine the analgesic effects of repeated doses of sucrose for human neonates over time. In the present study, the most immature neonates experienced the most painful procedures. Although the

neuroanatomical and neurochemical capacity to respond to pain is developed by mid gestation, the descending inhibitory mechanisms of preterm neonates to modulate pain are immature. Therefore, the neonates who experience the most pain are at greatest risk for adverse consequences. The central sensitivity and “wind-up” phenomena resulting from repeated pain transforms all stimuli into painful stimuli, thereby contributing to potential chronic or neuropathic pain (Fitzgerald, 2000; Plotsky et al., 2000). Although it is not ethical to examine the long-term effects of repeated pain in the most vulnerable neonates, studies examining consistent pain management, using safe and efficacious interventions, are required. These data would further support the use of these consistent pain interventions in clinical practice.

The focus of most studies to date has been the efficacy of sucrose for heel lances. Although in the current study, a significant reduction in PIPP scores was found with the administration of sucrose and NNS, pain associated with heel lances was not completely eliminated (as PIPP scores remained above 6). It still remains to be determined as to whether these statistically significant results are clinically important for preterm and term neonates experiencing a heel lance. Therefore, ongoing research to examine the most efficacious and safe interventions to reduce procedural pain in preterm and term neonates is required. Other pharmacological, behavioral and physical interventions may be required to eliminate the pain associated with heel lances and decrease PIPP scores closer to 0.

Data from this study further suggest that neonates experience many painful procedures in the NICU. Further research studies, using sucrose and NNS (alone or in combination with other interventions), for a variety of painful and non-painful procedures such as eye exams, intubations, lumbar punctures or venepunctures must be undertaken. Painful conditions such as NEC, birth injuries or asphyxia should also be considered. Future studies examining the clinical importance of pain reduction in neonates are required. In light of neonates' inability to

self-report pain, a priori consideration of clinical significance from parents' and caregivers' may provide direction to the assessment and management of neonatal pain.

Technician skill or expertise performing the painful procedure may influence pain responses. Studies that evaluate potential relationships between technician experience and pain responses for neonates of varying ages are required. Similarly, choosing the most appropriate technique or method of performing the painful procedure may affect pain responses. Shah, Taddio, Bennet & Speidel (1997) found that pain responses, as measured by NIPS scores, were higher in the heel lance group compared to the venepuncture group. Although the sample size was small ($n = 27$), and the study interventions were not blinded, the results suggest that alternative methods of obtaining blood should be considered. In a systematic review that identified two trials comparing term neonates' pain responses to venepunctures and heel lances, Shah and Ohlsson (2000) found that venepunctures, when performed by trained phlebotomists, decreased cry duration and pain scores. Larger studies with a more heterogeneous population and a validated composite measure of pain are required.

Many painful procedures in the NICU can be avoided and/or eliminated. Alternatives to repeated venipunctures or heel lances include the use of indwelling catheters or continuous transcutaneous monitoring. Future studies comparing the immediate and long-term safety and efficacy of alternative methods of monitoring neonates' status as well as the neurobehavioral outcomes for these neonates are required. In addition, studies that critically evaluate the rationale for all painful procedures in the NICU are required. Many procedures are performed with little or no evidence of their utility or efficacy. Studies examining health care providers' rationales for practice may provide insight into why procedures, such as bi-weekly routine blood work on all preterm neonates, are done. These data may provide direction for change in practice resulting in the elimination of all non-essential painful procedures in neonates.

Conclusion

There is sufficient data to support neonates' capacity for transduction, transmission, perception and modulation of painful stimuli. Although neonates' responses to pain do not fit with the IASP definition (IASP, 1979), their physiological and behavioral indicators are recognized as valid measures of pain. Over the past decade, several measures of pain have been developed, however, few measures have established psychometric properties for preterm and acutely ill neonates. The Premature Infant Pain Profile (PIPP) has established reliability and validity as well as beginning clinical utility for procedural pain measurement in preterm and term neonates. The PIPP includes both physiological and behavioral indicators as well as contextual indicators such as behavioral state and gestational age that are known to affect pain responses. The multidimensionality of the PIPP is congruent with the complex and multidimensional concept of pain.

Preterm and acutely ill neonates experience many painful procedures during their stay in the NICU. Although the immediate responses to pain may be protective at times, data on long-term effects of repeated or chronic pain suggest that permanent neuronal changes can occur. Due to the frequency of painful procedures in the NICU and the potential risks of repeated pain, it is essential to manage pain with interventions that are safe and effective. The administration of sucrose with or without NNS had been examined in several studies, however, the dose of sucrose or method of administration to a wide range of gestational ages was not known. This current study was designed to examine the safety and efficacy of sucrose for a variety of gestational ages, using a valid, multidimensional measure of pain.

The purpose of this study was to evaluate the safety and efficacy of sucrose and NNS for heel lances in preterm and term neonates. A reduction in PIPP scores was selected as the primary outcome. One hundred and ninety neonates were randomly allocated to receive sucrose and NNS, sucrose alone or water and NNS. Stratification for gestational age was used to control for the effects of age on the primary outcome. Groups were similar at randomization. There were no differences between groups in birth weight, SNAP: PE scores, number of painful procedures or days of life at study session. The Gate Control Theory of pain (Melzack & Wall, 1965) and an understanding of neuroanatomy and physiology served as a framework to explain the possible benefits of sucrose and NNS for a wide range of gestational ages.

PIPP scores in the sucrose and NNS groups were significantly lower than sucrose alone ($p = 0.007$) or water and NNS ($p < 0.001$) groups. Similarly, individual indicators of pain that comprise the PIPP, including brow bulge, eye squeeze, nasolabial furrow, heart rate and oxygen saturation were significantly lower in the sucrose and NNS group compared to the other two intervention groups. There were six adverse events during the study period, however, all of the events recovered spontaneously and no medical or nursing interventions were required. None of the adverse events occurred in the sucrose and NNS group.

The exploratory question addressed the effects of gestational age on the safety and efficacy of sucrose and NNS. Although the study was not sufficiently powered to detect significant differences between gestational age strata, the results of this study suggest that irrespective of gestational age, sucrose and NNS is more efficacious than sucrose alone or water and NNS. Differences within age strata were beyond the scope of this study.

The multidimensional nature of pain is evident in the hierarchical regression model for PIPP scores. This model helped to explain a significant degree of variability of the primary outcome. Intervention group contributed to the largest variance for PIPP scores (9%), with

gender contributing another 3%. The contribution of birth weight, severity of illness or number of painful procedures prior to the study did not contribute to PIPP scores. The contribution of gender was a serendipitous result that gives direction to future research. There are insufficient data from the present study to determine gender-specific efficacy of sucrose and NNS.

An important contribution of this study was the demonstration of the nature and incidence of adverse events with the administration of sucrose within different gestational age strata. Results of this study indicate that adverse events occur most frequently in the least mature neonates ($n = 4$), with one neonate choking on the pacifier and three neonates desaturating during the heel lance procedure. The increased frequency of adverse events is inversely proportional to gestational age. These findings are not surprising given the less mature Hypothalamus-Pituitary-Adrenal axis responses of preterm neonates.

Another contribution of this study is the multidimensional description of pain responses of preterm neonates of varying gestational ages. Included in this multidimensional description was the assessment of individual physiological and behavioral components of the PIPP. Few other studies have described the unidimensional and multidimensional responses to pain using an ANOVA. Results of this study indicate that both physiological and behavioral indicators provide important information about pain but some individual indicators (brow bulge, eye squeeze, maximum heart rate) may be more predictive of pain responses in the extreme preterm neonate. Further research concerning the contribution of each individual indicator for varying gestational ages is required.

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Appendix A

Physiological and behavioral indicators of pain in neonates

Physiological and Behavioral Responses to Painful Stimuli

Physiologic indicators	Research study	Comments
Increases in heart rate (HR)	Anand & Ansley-Green, 1985 Anand & Hickey, 1987 Anand et al., 1989, 1992 Bucher et al., 1995 Campos, 1994 Craig et al, 1993 Field & Goldson, 1984 Franck, 1986 Grunau et al., 1990 Gunnar et al., 1992 Johnston et al, 1993, 1997 Johnston & Strada, 1986 Johnston & Stevens, 1996 Marchette et al., 1991 Masciello, 1990 Maxwell et al., 1987 Oberlander et al., 2000 Owens & Todt, 1984 Porter et al., 1986, 1988, 1999 Stevens & Johnston, 1994 Taddio et al., 1995, 1997 Yaster & Maxwell, 1993 Williamson & Williamson, 1983	HR is the most frequently reported physiologic indicator of pain. Significant increases in HR were reported between the baseline and invasive tissue-damaging stimuli
Increases in heart rate variability	Field & Goldson, 1984 McIntosh et al., 1993	Significant changes in HR variability has been found in some studies

Physiological and Behavioral Responses to Painful Stimuli

Physiologic indicators	Research study	Comments
Decreases in oxygen saturation	Masciello, 1990 Maxwell et al., 1987	Significant changes in oxygen saturation have been found in some studies
Decreases in transcutaneous oxygen tension (TcPO ₂)	Craig et al., 1993 Gibbons & Swedlow, 1986 Marchette et al., 1991 Pickler et al., 1996 Porter et al., 1998 Pokela, 1994 Raju et al., 1980 Rawlings et al., 1980 Stevens & Johnston, 1994 Williamson & Williamson, 1993	Significant decreases in TcPO ₂ were reported during circumcision, heel lance, lumbar puncture and intubation in both term and preterm neonates
Changes in respiratory rate	Craig et al., 1993 Field & Goldson, 1994 McIntosh et al., 1993	Significant changes have been found in respiratory rate in some studies, although the direction of the changes have not been consistent
Changes in blood pressure (BP)	Anand & Ansley-Green, 1985 Anand & Hickey, 1987 Anand & al., 1989, 1992 Durand et al., 1989	Significant changes in BP were reported in term and preterm neonates

Physiological and Behavioral Responses to Painful Stimuli

Physiologic indicators	Research study	Comments
Changes in blood pressure	Kelly & Finer, 1984 Marshall et al., 1982 Marchette et al., 1991 Yaster & Maxwell, 1993	
Increase in intracranial pressure (ICP)	Durand, 1984 Johnston et al., 1993 Raju et al., 1980 Stevens et al., 1994	Significant ICP increases with awake intubation and heel lances in term and preterm neonates.
Palmar sweating	Harpin & Rutter, 1982 Geldaly-Duff, 1988	Neonates < 37 weeks gestation do not produce sweat
Stress hormones (catecholamines, growth hormones)	Anand et al., 1989, 1992 Anand & Anyshley-Green, 1985 Anand & Hickey, 1987 Cohen et al. 1991 Giannakouloupos et al., 1994 Guinsberg et al., 1998 Gunnar, 1992 Gunnar et al., 1981 Kehlet et al., 1980 McGrath & Unruh, 1987 Orsini et al., 1996 Teixeira et al., 1996	Significant increases in stress hormones have been found in preterm and term neonates. Responses are not specific to pain

Physiological and Behavioral Responses to Painful Stimuli

Behavioral indicators	Research study	Comments
Increased facial activity	Craig et al., 1993 Grunau & Craig, 1987, 1990 Guinsburg et al., 1998 Johnston & Strada, 1986 Johnston & Stevens, 1996 Ramenghi et al., 1996 Rushforth & Levene, 1994 Shah et al., 1997 Stevens et al., 1994, 1999 Taddio et al., 1997 Zahr & Balian, 1995	Significant increase in individual facial actions were reported between baseline and the tissue-damaging phase
Cry	Abad et al., 1993, 1996 Allen et al., 1996 Barr et al., 1994 Blass & Hoffmeyer, 1991 Campos, 1994 Fuller, 1991 Fuller & Horii, 1988 Gormally et al., 1996 Johnston & O'Shaughnessy, 1988 Johnston & Strada, 1986 Johnston et al., 1997 Lester, 1984 Lester & Zeskind, 1979	Significant increases in several cry domains. Cry most commonly noted in term neonates. Cry is only present in 50% of the time for preterm neonates

Physiological and Behavioral Responses to Painful Stimuli

Behavioral indicators	Research study	Comments
Cry	<p>Michelsson et al., 1982, 1983 Owens & Todt, 1984 Porter et al., 1986 Ramenghi et al., 1996 Smith et al., 1992</p>	
Increases in body movement	<p>Anand, 1993 Craig et al, 1993 Fitzgerald et al, 1989 Franck, 1986 Grunau et al., 2000 Johnston & Strada, 1986 Walden, 1997</p>	Gross motor activity is more pronounced during painful procedures but the quality of movement is dependent on gestational age
Inability to regulate behavioral state	<p>DiPietro et al., 1994 Gedaly-Duff et al., 1994 Pickler et al., 1996</p>	Behavioral stress and inability to regulate states are evident in painful situations. Regulation is dependent on gestational age.

Note. Adapted by Stevens et al. (2000a)

Appendix B**The Premature Infant Pain Profile
(PIPP)**

PREMATURE INFANT PAIN PROFILE (PIPP)

B. Stevens, C. Johnston, P. Petryshen, A. Taddio (1996). The premature infant pain profile:
Development and initial validation. *The Clinical Journal of Pain*, 12(1), 13.22.

PROCESS	INDICATOR	0	1	2	3	SCORE
<i>Chart</i>	Gestational Age (at time of observation)	36 weeks and more	32 weeks to 35 weeks, 6 days	28 weeks to 31 weeks, 6 days	less than 28 weeks	
<i>Observe Infant 15 sec</i> <i>Observe baseline: Heart Rate _____</i> <i>Oxygen saturation _____</i>	Behavioral State	active/awake eyes open facial movements crying (with eyes open or closed)	quiet/awake eyes open no facial movements	active/sleep eyes closed facial movements	quiet/sleep eyes closed no facial movements	
<i>Observe Infant 30 sec</i>	Heart Rate Max. _____	0 to 4 beats/ minute increase	5 to 14 beats/ minute increase	15 to 24 beats/ minute increase	25 beats/minute or more increase	
	Oxygen Saturation Min. _____	0 to 2.4% decrease	2.5 to 4.9% decrease	5.0 to 7.4% decrease	7.5% or more decrease	
	Brow Bulge	None 0-9% of time	Minimum 10-39% of time	Moderate 40-69% of time	Maximum 70% of time or more	
	Eye Squeeze	None 0-9% of time	Minimum 10-39% of time	Moderate 40-69% of time	Maximum 70% of time or more	
	Nasolabial Furrow	None 0-9% of time	Minimum 10-39% of time	Moderate 40-69% of time	Maximum 70% of time or more	

**TOTAL
SCORE**

Appendix C**Study Explanation and Consent Form**

Letterhead

Title: The Safety and Efficacy of Sucrose for Relieving Procedural Pain in Infants

Investigator: _____, RN, Ph.D. nursing student under the supervision of Dr.
 _____ RN, Ph.D. Professor in the Graduate Department of Nursing Science at the

Purpose of the Research: Babies admitted into Neonatal Intensive Care Unit's (NICU's) have many procedures that may be painful. It is important to identify a safe treatment for relieving pain in babies. The use of sugar water has been shown to reduce the pain from many of the procedures that babies have. Sucking on a soother with sugar water may further reduce pain. The purpose of this study is to identify whether sugar water alone or with a soother is safe and effective for babies.

Description of the Research: We are collecting information on babies at a time when they have a procedure that is painful (heel lance). All infantneonates born in Canada must have blood taken from their heel during the first week of life to look for possible diseases that may be curable. No blood work will be done specifically for research purposes. If you agree to enroll your baby in the study, your baby will receive one of three treatments: (a) sugar water given to your baby from a dropper, (b) sugar water given to your baby from a dropper and then providing him/her with a soother or (c) sterile water given to your baby from a dropper and then providing him/her with a soother. The treatment your baby receives is determined by chance (like the toss of a coin).

After your baby has received one of the three treatments, he/she will be videotaped before, during and 5 minutes after the blood test. Your baby's heart rate and oxygen requirements will be recorded from monitors the baby is attached to. We would also like to review your baby's chart to obtain details about your baby's birth history and general health status.

Potential Harms, Injuries, Discomforts or Inconveniences: There are no known harms associated with participation in this study. There may, however, be unforeseen harmful consequences.

Potential Benefits: Standard NICU care for neonates who experience a heel lance does not involve pain relief. The benefits of participating in this study may include pain relief from sucrose.

Confidentiality: Confidentiality will be respected and no information that discloses the identity of your baby will be released or published without consent except if required by law. For your information, the research consent form will be inserted in the patient health record.

Participation: Participation in the study is voluntary. If you choose not to participate, you and your baby will continue to have access to quality care. If you choose on behalf of your baby to

participate in this study you can withdraw your baby from the study at any time. Again, you and your baby will continue to have access to quality care.

I _____ have been asked to participate in a study conducted by _____ Ph.D. nursing student at the University of Toronto. The study is under the supervision of Dr. _____, University of Toronto. Graduate Department of Nursing Science.

I acknowledge that the research procedures described above have been explained to me, and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care for my child and for other members of my family. As well, the potential harms and discomforts have been explained to me and I also understand the benefits of participating the research study. I know that I may ask now, or in the future, any questions I have about the study or the research procedures. I have been assured that records relating to my child and my child's care will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission unless required by law

I hereby consent for my child
to participate in the study

Name of parent

Signature

The person who have be contacted
about the research is

Who may be reached at:

Signature

Date

I hereby consent for my baby _____ to be taped/photographed during participation in this research project. I understand that if I agree to participate I am free to withdraw my baby from the study at any time without compromising the quality care for me, my baby and for other members of my family.

I hereby consent for my child
to be taped/photographed

Name of parent

Signature

The person who have be contacted
about the research is

Who may be reached at:

Signature

Date

Appendix D**CHART ABSTRACTION SHEET**

**One-Time Management of Procedural Pain
Chart Abstraction Sheet**

Infant Study Number: _____

Study Group: _____

Infant Data:

1. Did the mother labour? ☐ 1 Yes
☐ 2 No

2. Start of labour: day _____ month _____ year _____ time _____ : _____

3. Type of delivery: ☐ 1 Spontaneous Vaginal
☐ 2 Vacuum Assisted
☐ 3 Forceps Assisted
☐ 4 Breech
☐ 5 C-section → Reason _____

4. Analgesia/Anesthesia: ☐ 1 None
☐ 2 Epidural
☐ 3 Spinal
☐ 4 General
☐ 5 Other: _____

5. Date & time of birth: day _____ month _____ year _____ time _____ : _____

6. Gestational Age at birth: _____ weeks _____ days

7 Birthweight: _____ grams

8. Sex: ☐ 1 Male
☐ 2 Female

9. Apgar Score: _____ @ 1 min _____ @ 5 min

10. Multiple: ☐ 0 No
☐ 1 Yes # _____

**One-Time Management of Procedural Pain
Study Session Data Sheet**

Infant Study Number: _____

	Study Session
1. Study Session: Date Time	_____ _____ _____
2. Weight	_____ grams
3. SNAP:PE score	_____
4. Last painful procedure: Date Time	_____ _____
5. Last feeding: Date Time	☐ 1 Fed ☐ 2 NPO ☐ 3 Continuous _____ _____
6. Last analgesic dose: Date Time Type Leave blank if none given.	_____ _____ _____
7. Behavioural state at beginning of session	☐ 1 Quiet sleep ☐ 2 Active sleep ☐ 3 Quiet awake ☐ 4 Active awake
8. Individual drawing blood	_____
9. Amount of blood taken	_____ cc
10. Immediate adverse events: - HR > 200 for 15 seconds or longer - HR < 80 for 15 seconds or longer - RR > 80 for 15 seconds or longer - RR < 20 for 15 seconds or longer - O ₂ sat < 80 for 15 seconds or longer - choking/gagging/coughing on solution - choking/gagging/coughing on pacifier Please comment if answer is Yes.	<div style="display: flex; justify-content: space-between;"> <div> ☐0 No ☐0 No ☐0 No ☐0 No ☐0 No ☐0 No ☐0 No ☐0 No </div> <div> ☐1 Yes ☐1 Yes ☐1 Yes ☐1 Yes ☐1 Yes ☐1 Yes ☐1 Yes ☐1 Yes </div> </div>

One-Time Management of Procedural Pain
Painful Procedures Data Sheet #1

Infant Study Number: _____

Cumulative Frequencies	By Study Session
1. Heel stick(s)	☐ 1 Yes → _____ ☐ 0 No
2. Venous stick(s) and/or # of attempts	☐ 1 Yes → _____ ☐ 0 No
3. Arterial stab(s) and/or # of attempts	☐ 1 Yes → _____ ☐ 0 No
4. IM/SC injection(s)	☐ 1 Yes → _____ ☐ 0 No
5. Peripheral IV start and/or # of attempts to start	☐ 1 Yes → _____ ☐ 0 No
6. Peripheral arterial line insertion and/or # of attempts to insert	☐ 1 Yes → _____ ☐ 0 No
7. Peripheral arterial line removal	☐ 1 Yes → _____ ☐ 0 No
8. Long line insertion and/or # of attempts to insert	☐ 1 Yes → _____ ☐ 0 No
9. Long line removal	☐ 1 Yes → _____ ☐ 0 No
10. Bladder tap and/or # of attempts	☐ 1 Yes → _____ ☐ 0 No
11. Chest tube insertion and/or # of attempts	☐ 1 Yes → _____ ☐ 0 No
12. Chest tube removal	☐ 1 Yes → _____ ☐ 0 No
13. Lumbar puncture and/or # of attempts	☐ 1 Yes → _____ ☐ 0 No
14. Tape removal <u>from</u> baby's skin	☐ 1 Yes → _____ ☐ 0 No

One-Time Management of Procedural Pain
Painful Procedures Data Sheet #2

Infant Study Number: _____

Cumulative Frequencies	By Study Session
15. TCPO ₂ /TCPCO ₂ probe removed from skin and/or skin site for probe changed	☐ 1 Yes → _____ ☐ 0 No
16. Clean superficial skin abrasion	☐ 1 Yes → _____ ☐ 0 No
17. Intrauterine transfusion	☐ 1 Yes → _____ ☐ 0 No
18. Endotracheal/NP tube insertion and/or # of attempts to insert	☐ 1 Yes → _____ ☐ 0 No
19. NG/OG tube insertion	☐ 1 Yes → _____ ☐ 0 No
20. Suctioning	☐ 1 Yes → _____ ☐ 0 No
21. Surfactant administration	☐ 1 Yes → _____ ☐ 0 No
22. Umbilical line insertion and/or attempt(s) to insert	☐ 1 Yes → _____ ☐ 0 No
23. Other: _____ (please specify)	☐ 1 Yes → _____ ☐ 0 No
24. Other: _____ (please specify)	☐ 1 Yes → _____ ☐ 0 No
25. Other: _____ (please specify)	☐ 1 Yes → _____ ☐ 0 No

Appendix E

Psychometric properties of The Premature Infant Pain Profile

Summary of Studies Evaluating Psychometric Properties of the PIPP

Study/Design	Population	Interventions	Results
Stevens et al., 1996 Descriptive, Correlational	1) n = 124 (32 - 34 weeks) 2) n = 39 (32 - 34 weeks) 3) n = 48 (28 - 30 weeks) 4) n = 27 (37 - 40)	1) Heel lance vs handling 2) Heel lance vs. handling 3) Heel lance vs. sham 4) Circumcision (baseline vs clamp)	1) Significantly lower PIPP scores for handling ($t = 12.24$, $p < 0.001$) 2) Significantly lower PIPP scores for handling ($t = 2.4$, $p = 0.02$) 3) Significantly lower PIPP scores for sham ($t = 2.6$, $p = 0.02$) 4) Significantly lower PIPP scores for clamp ($t = 2.6$, $P < 0.02$) No inter/intra rater reliability reported
Ballantyne et al., 1999 Cross-over	n = 43 (24 - 40 weeks)	Random order of 3 interventions (a) baseline, (b) pain event and (c) non-pain event	Significantly higher PIPP scores in pain event vs. non-pain event or baseline ($F = 4.8$, $p < 0.001$) Inter rater (0.93-0.96) Intra rater (0.94-0.98)
Walden, 1997 Descriptive	n = 11 (24 - 26 weeks)	PIPP scores computed for heel lances weekly for 6 weeks (phases of lance: Baseline, lance, squeeze, return to base)	PIPP scores lowest during baseline phase of heel lance for all gestational ages except 27 weeks (all $p < 0.005$) at all times
Beyer et al., 2000 (abstract quality) Comparison of PIPP	n = 10 (< 36 6/7 weeks) n = 11 (>37 weeks)	Two raters computed PIPP scores (a) pre-op, (b) post-op before analgesia (c) post-op after analgesia	PIPP demonstrated high inter-rater reliability and validity (no statistics) for (a) and (b) but not (c)
Johnston et al., 1999 RCT	n = 48 (25 - 34 weeks)	Single dose sucrose vs. triple doses sucrose vs. water for heel lances	Significantly lower PIPP scores in triple dose ($F = 9.14$, $p < 0.001$)
Stevens et al., 1999 RCT	n = 122 (27 - 31 weeks)	Sucrose and NNS vs. Water and NNS vs. positioning for all painful procedures	PIPP scores in both pacifier groups significantly lower than control group (all p values < 0.003)

Appendix F

Correlational co-efficients for regression models

Correlation Co-efficients of Neonatal Variables Prior to Randomization

Variable	Apgar 5	SNAP: PE	# invasive procedures	Gestational age	Birth weight
Apgar 5	1.00	0.4	0.04	0.2	0.17
SNAP: PE	0.4	1.00	0.12	0.54	0.55
#invasive procedures	0.04	0.12	1.00	0.2	0.2
Gestational age	0.2	0.54	0.2	1.00	0.9
Birth weight	0.17	0.55	0.2	0.9	1.00

Regression co-efficients for neonatal variables prior to randomization

Model	B	Std. Error	t	Sig
Female	-1.05	0.42	-2.50	0.01
Sucrose and NNS	-2.79	0.56	-4.91	0.001
Sucrose alone	-0.75	0.57	-1.41	0.16