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An Evaluation of the Efficacy of Selected Nonpharmacologic Pain Interventions in Infants

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AN EVALUATION OF THE EFFICACY OF SELECTED NONPHARMACOLOGIC PAIN INTERVENTIONS IN INFANTS

by

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Abstract

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Infants subjected to painful stimuli respond with deleterious physiologic and metabolic effects, behavioral changes, and potentially long term effects on painful stimuli processing and response. There are few studies that address effective pain interventions for infants, particularly those interventions that staff nurses can implement independently. Interventions must be identified and their effectiveness must be validated for this vulnerable population.

Pharmacologic management of pain may cause deleterious side effects and needs to be ordered by physicians or nurse practitioners. Nonpharmacologic methods to manage pain can usually be implemented by staff nurses independently. This study evaluated the efficacy of two nonpharmacologic pain management interventions, sucking and sucrose, and their ability to potentiate each other.

This study is based on the Gate Control Theory of pain which posits that benign stimuli, such as sucking, send messages to the central nervous system that compete with painful stimuli to decrease the amount of pain perceived. Sucrose is thought to be mediated through opioid pathways. A sucrose coated pacifier may reduce pain via two pathways, thus being more effective than uni-modal techniques.

A randomized, complete block, experimental design was used to evaluate the pain reduction efficacy of: a sucrose coated pacifier, oral sucrose solution, water moistened pacifier, and no intervention. Eighty-four neonates undergoing the painful procedure of heelstick were studied. Pain measures were duration of cry, vagal tone, and salivary cortisol.

MANOVA revealed that the sucrose coated pacifier group cried significantly less than the water moistened pacifier and control groups. ANCOVA demonstrated significant covariation of birth weight with cortisol and procedure length with cry, neither covariate impacted treatment main effects. Repeated measures ANOVA revealed that the sucrose coated pacifier group demonstrated significantly lower vagal tone during heelstick than did the oral sucrose solution and no intervention groups. This significant difference persisted for 15 minutes post heelstick between the sucrose coated pacifier and no intervention groups. In summary, this study demonstrated the clinical efficacy of offering a sucrose coated pacifier to manage pain during heelstick in healthy neonates.

To Bobbie,

I will miss you always.

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Lastly, appreciation is expressed to all the parents who consented to having their infants participate in this study. May this work help to improve the management of pain in this most vulnerable population.

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CHAPTER 1: The Problem

Background of the Problem

Historically, it has been held that infants do not experience pain due to neurologic immaturity. This false belief has been compounded by the fact that infants cannot report their pain experience in adult terms. Even if someone believed that an infant was experiencing pain, analgesics were withheld because it was felt that it was too dangerous to give these agents due to the potential respiratory and cardiovascular side effects. Thus, many infants were, and occasionally still are, subjected to unanesthetized surgeries or painful procedures using only paralyzing agents, without the use of analgesics (Butler, 1989; Cunningham, 1990).

Considerable literature exists that substantiates the effectiveness of pharmacologic agents in pain relief and suppression of the stress response in reaction to nociceptive stimuli in infants (Anand & Carr, 1989; Anand, Sippell, & Aynsley-Green, 1987; Berde, 1993; Bhatt-Mehta & Rosen, 1991; Eland, 1988; Krane, Jacobson, Lynn, Parrot, & Tyler, 1987). Less information is available that focuses on the effectiveness of non-pharmacologic methods for pain or stress relief in infants (Beaver, 1987; Blass & Hoffmeyer, 1991; Broome & Tanzillo, 1990; Campos, 1989; Collins & Kuck, 1991; Field & Goldson, 1984; Kimble, 1992; Smith, Fillion, & Blass, 1990).

Nurses haphazardly implement various interventions, believing that they may have some pain alleviating properties based on anecdotal evidence. Research is needed regarding the actual efficacy of interventions. The ability of various interventions to potentiate each other also needs to be explored.

Statement of the Problem

Neuroanatomic structures necessary for transmission of pain impulses are present in the fetus (Anand & Carr, 1989). Immaturity in the pathways for transmission of the impulse and lack of inhibitory processes for such suggest that the infant may even be hyperalgesic (Fitzgerald, 1991b). Infants subjected to painful stimuli respond with deleterious physiologic and metabolic effects as well as behavioral changes and potentially negative long term effects on nociceptive stimuli processing and response (Anand & Hickey, 1987).

Administration of opioids can modify the pain experience, but there has been reluctance to use opioids in infants due to concerns about the safety and metabolism of the drugs. Opioids can be used in neonates but this population is more susceptible to the depressant effects of the drugs thus opioids must be used with caution (Bhatt-Mehta & Rosen, 1991). Opioid clearance approaches adult rates by one to two months of age (Koren, Butt, Chinyanga, Soldin, Yok-Kwang, & Pape, 1985). A cautious interpretation of the literature suggests opioid administration should begin with a reducing the initial dose of medication and intensive monitoring throughout the administration time frame for infants up to six months of age, even to one year of age (Acute Pain Management Guideline Panel, 1992).

Initial research suggests that sucrose may be mediated through the opioid pathway (Blass, Fillion, Rochat, Hoffmeyer, & Metzger, 1989; Blass, Fitzgerald, & Kehoe, 1987) therefore possessing some pain alleviating properties. Given the risk of opioid administration in neonates, sucrose may provide a lower risk alternative with similar efficacy.

Blass and Hoffmeyer (1991) studied human neonates and suggested that sucrose may serve as an effective analgesic. Based on this study, health care providers have been offering infants pacifiers coated with sucrose, in the form of table sugar, to provide analgesia during painful procedures. Blass and Hoffmeyer (1991) used a liquid sucrose solution in their study. It has not been shown that sucrose in the form of table sugar functions in a manner similar to a liquid sucrose solution, though a theoretical argument can be made for such administration. It is also necessary to distinguish between effects of sucrose administered through a syringe versus a pacifier. Sucking alone may attenuate pain distress behaviors and have a pacifying effect (Campos, 1989; Field & Goldson, 1984; Kimble, 1992; Miller & Anderson, 1993).

Purpose of the Study

The aim of this study was to investigate the efficacy of selected nursing interventions in alleviating acute, short term, mildly noxious procedural pain in neonates. This study examined the use of sucrose as an effective intervention for pain relief. It also analyzed the interaction between sucrose administration and the possible potentiating effects of sucking by exploring route of administration: syringe versus pacifier.

Hypotheses

The major hypothesis tested in this research was:

- **infants offered a sucrose coated pacifier demonstrate decreased pain behaviors when undergoing painful procedures compared to infants undergoing painful procedures who are offered sucrose solution via a syringe, a water moistened pacifier, or no intervention.**

Sub-hypotheses were:

H_1: **infants offered a sucrose coated pacifier demonstrate decreased pain behaviors when undergoing painful procedures compared to those who are offered no intervention,**

H_2: **infants offered a sucrose solution demonstrate decreased pain behaviors when undergoing painful procedures compared to those who are offered no intervention,**

H_3: **infants offered a water moistened pacifier demonstrate decreased pain behaviors when undergoing painful procedures compared to those undergoing painful procedures who are offered no intervention,**

H_4 **infants offered a sucrose coated pacifier demonstrate decreased pain behaviors compared to those who are offered a sucrose solution,**

H_5 **infants offered a sucrose coated pacifier demonstrate decreased pain behaviors compared to those who are offered a water moistened pacifier.**

These are directional hypotheses based on previous research in rat pups, who have a pain model similar to humans (Blass, et al., 1987). Research in human neonates has also demonstrated the effectiveness of sucrose as an analgesic during painful procedures (Blass

& Hoffmeyer, 1991). In the current study it was hypothesized that sucrose plus sucking will be most efficacious in alleviating pain, sucrose alone next, sucking alone third and no intervention infants would demonstrate the most pain behaviors.

Definition of Terms

The independent variables in this study were the four treatment groups: water-moistened pacifier, sugar coated pacifier, 12% sucrose solution given orally, and routine care (no intervention or control).

The dependent variables in this study were duration of crying, vagal tone reactivity, and change in salivary cortisol after the painful procedure of heel lancing for the purpose of completing newborn metabolic screening.

The theoretical and operational definitions of terms used in this study were as follows:

Pain

theoretical: The expectation, correct or otherwise, that there is tissue damage and an unpleasant, subjective experience (Mersky & Spear, 1967) which is interpreted in terms of physiologic and behavioral manifestations. The emotional and subjective responses associated with pain are difficult to evaluate in neonates. Therefore, pain is defined in the restricted sense of nociception, the physiologic response of the pain reception neuron.

operational: Pain measured by calculation of duration of cry, change in salivary cortisol level, and change in vagal tone.

Neonate

theoretical: An infant from birth to 28 days of age.

operational: An infant birth to 72 hours of age, prior to discharge from the hospital after a normal birth.

Awake state

theoretical: One of six behavioral states in an infant, increasing in level of arousal from quiet sleep to crying (Brazelton, 1973).

operational: The infant is observed to be awake, with eyes open, responding to the environment with quiet or active movement.

Vagal tone

theoretical: A component of heart rate variability influenced by the parasympathetic nervous system, modulated via the vagus nerve. Postulated to be an index of pain in infants (Porter, Porges, & Marshall, 1988).

operational: Measured by electrocardiogram recording of heart rate which was downloaded to computer. The computer was programmed to sense the R wave in milliseconds for interbeat intervals to convert to heart periods and store to disk for later editing and analysis to determine the amplitude of respiratory sinus arrhythmia.

Crying

theoretical: A state of emotion, method of communication in infants, expressed by vocalizations including whimper, soft cry, loud cry, shriek, scream, wail, and sob.

operational: **Measured as duration of audible cry / distress vocalizations, the time period during and after painful procedure from when the infant starts crying until the infant stops crying.**

Cortisol

theoretical: **A steroid hormone secreted in response to stress.**

operational: **Measured by laboratory analysis of saliva samples obtained pre-procedure and 25 minutes post-procedure to allow for time course of the adrenocortical response.**

Delimitations of the Study

Eighty four infants were observed for this study. Only presumed healthy term neonates whose mothers were healthy and had no history of drug abuse were included. Data were collected between March 1, 1996 - September 27, 1996.

Significance of the Study

It was anticipated that sucrose administration via sucking on a sugar coated pacifier would decrease the amount of pain behaviors demonstrated during painful procedures over sucrose offered via syringe, sucking on a water moistened pacifier, or no intervention. If this hypothesis was supported, then offering a sucrose coated pacifier may be a non-invasive pain relieving intervention that has fewer side effects than narcotics or analgesics. It may also offer a new alternative to more standard, non-pharmacologic therapies such as positioning or distraction.

Offering a sucrose coated pacifier has advantages in that it can be done quickly and easily, is readily available, is inexpensive, and nurses can implement it as an independent

practice decision - all important considerations in today's health care economy. It is an intervention that can be used in any setting (e.g., in-patient, ambulatory). If sucrose decreases the number of demonstrated pain behaviors, possibly indicating a decreased amount of the subjective experience of pain, then the sparse number of pain interventions available for infants that nurses and parents can independently implement has been increased.

Increasing the number of effective nursing interventions has even further reaching significance when the physiologic consequences of pain are considered. A prolonged hyperalgesia has been demonstrated in term and preterm infants following repeated heelsticks which can be averted with application of topical anesthetic prior to tissue injury (Fitzgerald, Millard, & McIntosh, 1989). Because of the "plasticity" or changeability of the nervous system of the infant and young child, insults during this time period may negatively alter the final architecture of their adult pain system (Fitzgerald, 1991a).

One response to pain in infants is crying. Crying can be physiologically harmful. Crying in the neonate reestablishes fetal circulation in the heart by obstructing venous return in the vena cava (Anderson, 1989). This may contribute to hypoxemia and fluctuations in blood flow, increasing the potential for intracranial hemorrhage. Crying can cause tachycardia, decreased blood oxygen saturation, and negative changes in the endocrine system (Pineyerd, 1994). Effectively alleviating pain decreases the amount of crying and averts these negative outcomes.

Clinically, practitioners are using sucrose in the form of granulated (table) sugar for pain relief during procedures. The granulated sugar is administered by dipping the

pacifier in water, coating it with sugar, then offering the infant the pacifier. This technique differs from experimental studies that have demonstrated the potential pain alleviating properties of sucrose (Allen, White, & Walburn, 1996; Blass & Hoffmeyer, 1991; Bucher, et al., 1995; Haouari, Wood, Griffiths, & Levene, 1995; Miller, Barr, & Young, 1994). These studies have generally offered a liquid sucrose solution administered via syringe.

The study presented here varies from previous research in that the formulation of sucrose used is different. Table sugar was used in this study versus varying amounts of sucrose solutions in previous studies. Delivery of the sucrose has generally been studied via syringe, though one study (Blass & Hoffmeyer, 1991) delivered sucrose solution via pacifier before and during circumcision. The current study evaluates granulated sugar on a pacifier, sucrose solution orally, and sucking on a plain pacifier. The measures used to assess the pain experience in this study were more sophisticated than those used in previous studies, thus providing a more precise assessment of the pain experience.

The use of sucrose does not require a physician's or nurse practitioner's order, broadening the scope of independent nursing interventions for pain relief and ultimately benefitting the patient. This investigation was needed to provide an efficacious, research based practice. Health care institutions and providers are accountable for pain management (Acute Pain Management Guideline Panel, 1992). Increasing the available number of demonstrated effective pain relief interventions will facilitate achievement of this objective and result in more humane care for infants.

CHAPTER 2: Review of the Literature

The purpose of this study was to investigate the efficacy of selected non-pharmacologic nursing interventions in alleviating acute pain in neonates. In order to comprehend how these interventions may act to reduce or alleviate pain, the pain pathway must be understood. The pain experience is more than simply the transmission of nerve impulses, it also includes the organisms' response to the painful stimulus. It is an extremely complex phenomenon, and all the components that comprise it are not well elucidated. The most widely accepted theory of pain, at present, is the Gate Control Theory.

It is a common misperception that infants do not experience pain. A review of research substantiates the fact that infants do experience pain, perhaps to a greater degree than adults. Part of the problem in appreciating the pain experience of infants is the difficulty in assessing pain in this pre-verbal population. Methods of pain assessment and interventions for pain alleviation will be addressed as related to this study.

Theoretical Framework: The Gate Control Theory

The Gate Control Theory of pain purports that incoming nociceptive stimuli can be modified or even inhibited by a gating mechanism embedded in the dorsal horn of the spinal cord, the substantia gelatinosa (SG). This gate filters the incoming stimulus before it crosses over to the anterolateral cord and ascends through the spinothalamic tract to the

higher perceiving centers in the thalamus. Based on attention, emotion, and memory of prior experiences, nociceptive stimuli that reach the thalamus can trigger further modulation or gating of the impulse by way of descending fibers (Bonica, 1991; Melzack & Wall, 1965; Wall, 1978).

The Pain Pathway

The first stage of neural transmission is conduction of primary afferent impulses to the spinal cord. A peripheral nerve is made up of various axons. These are differentiated on the basis of size and the degree of myelination. They are classified into three major groups: Aα (6-22 millimicrons), Aδ (2-5 millimicrons), and C (0.3-3 millimicrons). A fibers are myelinated, with Aδ being thinly myelinated and able to conduct nerve impulses rapidly (5-100 meters per second); C fibers are unmyelinated and conduct much slower (less than 2 meters per second) (Berde, Anand, & Sethna, 1989; Fitzgerald & Anand, 1993; Schechter, 1985). Aα fibers respond to light mechanical stimuli such as gentle touch or pressure. The majority of Aδ and C fibers respond to nociceptive (painful) stimuli from mechanical, thermal, or chemical causes.

When afferent peripheral input reaches the dorsal horn, the SG acts as a gate to increase or decrease the amount of nociceptive impulses transmitted from the periphery to the central nervous system. The gate is partly mediated by the number of impulses transmitted via the Aα fibers. If enough Aα fiber impulses are transmitted, they activate the gate to close which prevents peripheral transmission from Aδ and C fibers to the dorsal horn. Ascending and descending stimuli from the thalamus combine to influence

impulse transmission from the dorsal horn (Figure 1, see Appendix A for copyright permission).

When subjected to stimuli such as occurs with tissue injury, cells in the dorsal horn demonstrate a lowered threshold (Woolf, 1991). In other words, stimuli which may not have been painful previously, are now perceived as painful with less stimulation needed to evoke this. This hypersensitivity is very responsive to treatment with opioids (Fitzgerald & Anand, 1993). Physiologically, this is logical since opioid receptors are concentrated in the gray matter of the spinal cord, especially in the dorsal horn (Anand & Carr, 1989).

The above description of the pain pathway has been studied in adults. It is thought that infants have a similar pain model but some variation exists. A review of research is warranted to clarify common misperceptions and highlight known differences.

The Pain Pathway in the Infant

A misperception has been propagated by the argument that infants are neurologically immature and thus cannot feel pain due to lack of myelination. In the adult, thinly myelinated or unmyelinated nerves conduct nociceptive impulses. Slowing of conduction velocity resulting from incomplete myelination in the neonate is balanced by the shorter interneuronal and neuromuscular distances the impulse has to travel (Anand & Carr, 1989). Additionally, by 30 weeks gestation, nerve tracts for pain transmission in the spinal cord and brain stem are completely myelinated up to the thalamus (Anand & Carr, 1989).

Young infants have a higher density of cutaneous afferent fibers present than adults do. These fibers are also closer to the surface of the skin (Fitzgerald, 1991a). The

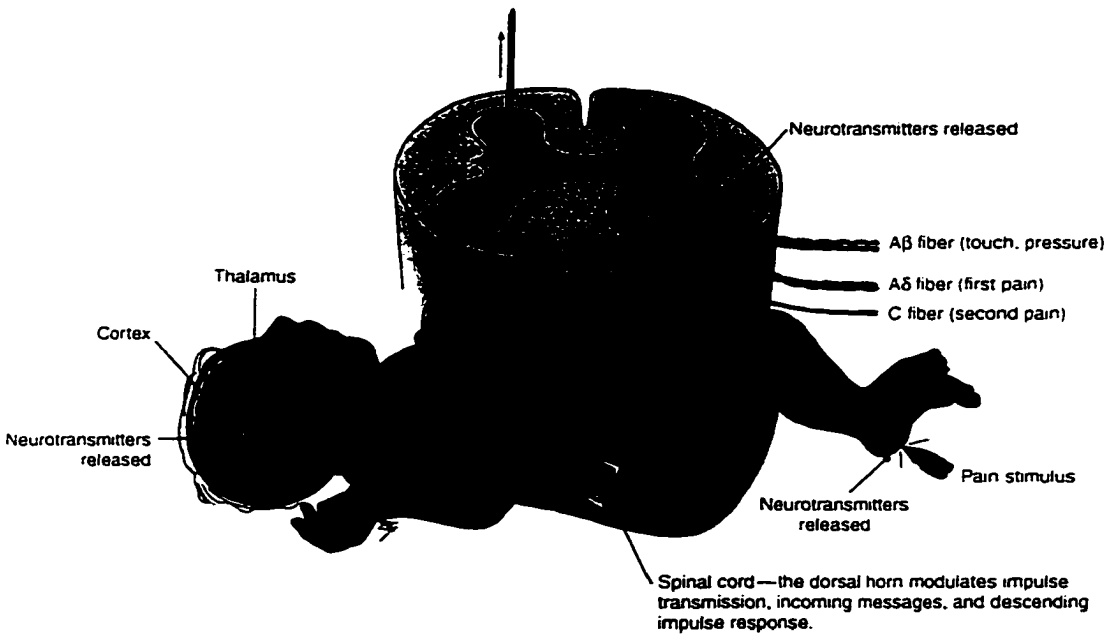

Figure 1. The pain pathway in an infant. From Greenberg, C. S. (in press). Pain in children. In V. Bowden, S. Dickey, & C. S. Greenberg (Eds.), Children and their families: The continuum of care. Philadelphia: W. B. Saunders. Used with permission.

density of fibers coupled with the unique skin structure of young infants permits more fibers to be stimulated by noxious stimuli. These fibers generate an action potential that travels to the dorsal horn. Studies in rats (who have a pain model similar to humans) show that, although C fibers are present in the dorsal horn, they do not produce postsynaptic spikes in the neurons until the end of the first postnatal week (Fitzgerald, 1991b). They do however produce subthreshold effects which increase sensitivity to subsequent stimuli. The importance of this lies in the fact that C fibers transmit much of the noxious input, so though the peripheral receptors recognize pain, they transmit it poorly and the signal seems to "linger" in the system. Neonates also lack some of the neurotransmitters that inhibit pain transmission (Fitzgerald & Anand, 1993). In summary, there is increased potential for afferents to transmit the nociceptive message, the message remains in the system longer, and there is lack of ability to inhibit pain impulse transmission. Thus, young infants most likely experience even more pain with the same stimulus than do adults.

Pain Assessment in Infants

Pain is a subjective, individualized experience. Because self-report is the most valid measure of this event, it is difficult to evaluate the exact experience of pain in a pre-verbal infant. Since self-report is not available from this population, other methods have been used in an attempt to ascertain the presence of pain in infants. A multidimensional approach provides the most accurate assessment of pain. One behavioral (cry) and two physiologic (vagal tone, salivary cortisol) measures were employed to evaluate the response to nociceptive stimuli in this study.

A conceptualization of pain that is based on a model of adult pain may not be appropriate for infants. The question arises: is it pain or stress that is being measured? Stress, or distress, and pain may cause the same responses in an infant, and it may be meaningless to try to distinguish between the two (Porter, 1993). Rather, it may be more therapeutic to identify the responses and appropriately intervene than to identify the exact origin of the distress.

Stress causes deleterious effects in the infant, whether due to pain or other stressors. These effects include physiologic responses such as vital sign changes, hormone secretion (Gunnar, Porter, Wolf, Rigatuso, & Larson, 1995), and immunologic dysfunction. Additionally, ongoing pain may cause a hyperalgesia in the area and alter the final architecture of the adult pain system. The extent of psychologic effects and the impact that pain has on complex behaviors in infants is not known. Sleep pattern disturbances (Anders & Chalemian, 1974; Emde, Harmon, Metcalf, Koenig, & Wagonfeld, 1971) and changes in the Brazelton Neonatal Behavioral Assessment Scale scores (Marshall, Stratton, Moore, & Boxerman, 1980) have been found.

Earlier born preterm infants demonstrated less behavioral responsiveness and poorer physiologic response (greater elevation of heart rate and lower oxygen saturation levels) when subjected to heelstick than preterm infants of later gestational age (32 weeks post conceptual age) (Johnston & Stevens, 1996). Infants who were cared for in Neonatal Intensive Care Units (NICUs) have anecdotally been reported to be hypervigilant, they tend to watch a caregiver's hands instead of making eye contact with the caregiver as most infants do. Parents of infants and toddlers who were in NICUs as

infants have anecdotally reported that their children do not like their heels to be touched (presumably conditioned from multiple heelsticks for blood draws).

In this study, measures were chosen that attempt to identify the presence of pain in infants. The reliability and validity of pain measures in infants are still under investigation. In reality, measures selected for this study may identify pain or a more general stress response. An infant who was quiet and apparently unstressed prior to administration of nociceptive stimuli was assumed to be responding to the pain of the inflicted stimuli during the data collection period.

Infant state. Grunau and Craig (1987), in a study of newborns reacting to the stimulus of a heel lance, noted a state dependent difference in that alert infants responded with significantly more facial movement than sleeping infants. Premature infants also showed state dependent changes in physiologic parameters, particularly heart rate, in response to heel lance. These changes were dependent on phase of the procedure (baseline, warming of the heel, stick, squeeze) and state, with higher heart rates seen with increasing levels of alertness and advancing phase of the procedure (Stevens & Johnston, 1994). Since state influences the observed degree of reaction to painful stimuli, it must be taken into account when assessing pain in infants.

Cry

Crying is a behavior that is one of the most widely accepted indicators of pain in infants (Porter, 1993). The cry of an infant generally evokes a response from its caretaker.

Cries associated with pain have been found to be spectrographically distinct from other cries such as those of hungry or fussy infants (Fuller, Horii, & Conner, 1989; Levine

& Gordon, 1982). Further study by Fuller (1991) suggests that the degree of discrete differences in types of cries may be minimal, based on percentage of accurately identified cries, implying that all may be points on a distress-arousal continuum.

Johnston, Stevens, Craig, and Grunau (1993) found spectrographic differences in the pain cries of varying aged infants when premature, term, and 2- and 4-month-old infants were studied. Premature infants' pain cries contain more characteristics that arouse the listener, though their facies demonstrate less pain characteristics, possibly due to muscle weakness or neurological immaturity. The authors do note that, due to ethical constraints regarding pain research, a clinical pain situation was used as the experimental pain stimulus. Thus, there were three different stimuli for premature, term, and older infants, possibly resulting in varying degrees of pain inflicted.

Pain cries may be distinguished by untrained adults (Porter, Miller, & Marshall, 1986), although training increases recognition of abnormal cries (Wasz-Hockert, Partanen, Vuorenkoski, Valanne, & Michelsson, 1964). Muller, Hollien, and Murry (1974) found that mothers could not discriminate between hunger, pain, or auditory startle cries. These authors concluded that the listener must rely on contextual cues to judge the eliciting stimulus. Therefore, one must also look at other measures of distress and the situational context in identifying a pain cry (Owens, 1984).

Clinicians frequently use cry as an indicator of pain in infants (Broome & Tanzillo, 1990; Franck, 1989; Fuller, Thomson, Conner, & Scanlon, 1996; Hultgren, 1990; Johnston & Stevens, 1990; Jones, 1989; Mills, 1989; Owens, 1986; Pigeon, McGrath, Lawrence, & MacMurray, 1989). Many studies have also used crying as a pain measure

(Allen, et al., 1996; Blass & Hoffmeyer, 1991; Campos, 1989; Grunau & Craig, 1987; Grunau, Johnston, & Craig, 1990; Gunnar, Connors, Isensee, & Wall, 1988; Johnston, et al., 1993; Johnston & Strada, 1986; Maunuksela, Olkkola, & Korpela, 1987; Owens & Todt, 1984; Rebesco, Cotler, & Jason, 1984). Because of the face validity, common use and acceptance of crying as a pain indicator, it was chosen as a behavioral indicator of pain in this study.

Vagal Tone

The homeostatic processes that regulate body functions demonstrate rhythmic increases and decreases within a certain range of normal. Generally, the greater the normal oscillation, the healthier the individual (Porges, Matthews, & Pauls, 1992). Heart rate is one such system. Heart rate is dependent on continuous feedback between the central nervous system and peripheral autonomic receptors, thus it is neurally mediated. Heart rate patterns are reflective of nervous system status. They are thought to be influenced by mental state such as alertness, attention, emotion, and stress (Porges & Byrne, 1992).

Two heart rate patterns have frequently been used to assess infant response to pain: heart rate and heart period. Heart rate is the number of times the heart beats per unit of time, usually minutes. Heart period is the amount of time between each successive heart beat (Owens, 1984). Use of heart rate and heart period may result in inaccurate conclusions since these patterns are influenced by both neural (e.g. vagal) and non-neural (e.g. baroreceptor) input.

Measurement of cardiac vagal tone, another heart rate pattern, employing respiratory sinus arrhythmia (RSA) eliminates the influence of non-neural factors and provide data that is more specific to the pain itself because RSA is directly influenced by central nervous system control (Porter 1989). RSA is a normal phenomenon where the heart rate slows during expiration and increases during inspiration. These shifts in heart rate are primarily mediated through the parasympathetic branch of the autonomic nervous system via the vagus nerve. They reflect the rhythmic "gating" of vagal effects on heart rate by respiration, and the magnitude of change is associated with vagal efferent tone to the heart. Therefore, the greater the RSA amplitude, the greater the vagal tone. In order to assess cardiac vagal tone, Porges (1985) developed a statistical technique for quantification of the amplitude of RSA using a unique time series method (see Chapter III, Procedures for discussion of this technique). The vagal brake, which functionally slows heart rate by increased vagal output to the heart and inhibition of sympathetic influences (Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996), influences vagal tone reactivity. The vagal brake is a graded phenomenon, not all or none. Releasing the vagal brake reduces vagal inhibition on the heart thus increasing heart rate. Heart rate is not totally determined by the vagal brake. Therefore, changes in vagal tone and heart rate are not always highly correlated (Porges, et al., 1996).

Vagal tone provides information about central control of autonomic processes and by inference, information about central processes that are necessary for organized behavior (Porges, et al., 1992), individual response, and vulnerability to stress (Porges, 1995). Vagal tone is sensitive to environmental demands and stimulation, and decreases

during attention demanding tasks such as sucking, feeding (Porges & Lipsitt, 1993) and concentration on visual stimuli (Richards, 1987). Measurement of vagal tone during non-challenging baseline situations gives an indication of normal homeostatic functioning. Measurement during challenging or demanding situations gives an indication of the nervous system's ability to adapt (Porges & Byrne, 1992).

Ability to mount a strong vagal tone response to aversive stimuli is a reflection of better neurobehavioral organization in the newborn (Gunnar, et al., 1995). There is a strong relation between poor developmental outcome and low neonatal vagal tone (Fox & Porges, 1985) with low baseline vagal tone levels being affiliated with high-risk populations (Porges, 1992). Infants who showed initially lower resting vagal tones did not respond with as great a cardiac response to an assumedly painful procedure (Porter, et al., 1988) and had less optimal behavioral organization (Hofheimer, Wood, Porges, Pearson, & Lawson, 1995). In low birth weight infants, higher RSA was associated with better social skills, and greater RSA maturation was associated with better mental processing and gross motor skills (Doussard-Roosevelt, Porges, Scanlon, Alemi, & Scanlon, 1997). Knowledge of vagal tone reactivity may be helpful in identifying infants who are at greater risk for neurological complications, knowing that an organism's ability to self-regulate is an indication of an intact central nervous system.

Atypical vagal tone reactivity, even in the presence of normal baseline reactivity, appears to be associated with infants who have behavioral and regulatory problems (DiPietro & Porges, 1991; Porges, 1992). Infants who, at 9 months, demonstrated greater

decreases in vagal tone during social attention demanding tasks had fewer behavioral problems at 3 years of age (Porges, et al., 1996).

Studies have investigated the effect of pain on vagal tone. Vagal tone was significantly decreased during the stress of unanesthetized circumcision (Porter, Porges, & Marshall, 1988). Vagal tone and heart period decreased with increasing invasiveness of the procedure. The decrease in vagal tone was paralleled by increases in cry pitch, explainable by the fact that the laryngeal nerves are also innervated via the vagus. Quantifiable differences were found in the responses to pain stimuli compared to other stressors associated with the procedure such as restraint (Porter, et al., 1988).

When resting vagal tone was analyzed for predictive value, it was found that resting values were predictive of magnitude of response. Infants with higher resting values showed a greater magnitude of change during circumcision than infants with lower resting vagal tones (Porter, et al., 1988). The infants who seemed to react more may be at greater risk for adverse outcomes in response to painful procedures such as fluctuation in vital signs, crying, and hypoxic episodes potentially contributing to the occurrence of intraventricular hemorrhage. This has implications for pre-emptive pain management: treating pain before it causes detrimental effects.

Because of its correlation with physiologic (heart period) and behavioral (cry) indicators of pain in infants, vagal tone shows promise as an index of pain in infants (Porter, 1989). Another aspect that is beneficial, both for research and clinical application, is that cardiac vagal tone shows a rapid response to challenge (Porges & Byrne, 1992).

Cortisol

Pain is a stressor that precipitates a stress response. Hormonal and metabolic changes have been demonstrated in premature and term infants undergoing the stress of lightly anesthetized surgery. There is an increased secretion of catecholamines, growth hormones, glucagon, cortisol, and other corticosteroids (Anand, 1986; Anand & Aynsley-Green, 1988; Anand, et al., 1985; Anand, Hansen, & Hickey, 1990). Cortisol has been used as a measure of the adrenocortical response to the stress of painful procedures (Gunnar, 1992; Gunnar, Fisch, & Malone, 1984; Gunnar, Hertsgaard, Larson, & Rigatuso, 1992).

Early studies showed moderate, positive correlations between serum cortisol concentration and the neonate's behavioral state, with crying being the high end of the scale (Anders, Sachar, Kream, Roffwarg, & Hellman, 1970; Tennes & Carter, 1973). Unfortunately these studies did not look at change in cortisol level from baseline, so one cannot infer magnitude of change, which is the relationship most commonly studied (Gunnar, Fisch, Korsvik, & Donhowe, 1981).

Gunnar and colleagues have studied the relationship between behavioral distress and cortisol levels. Behavioral state has been related to cortisol levels. Cortisol levels obtained before stimulation are influenced by the behavioral state of a newborn in the 30 minutes prior to sampling (Gunnar, 1992). Quiet sleep was negatively correlated to cortisol with all awake states being positively correlated; cortisol levels are lower with sleep and increase with wakefulness (Gunnar, Malone, Vance, & Fisch, 1985). Salivary

cortisol elevations in response to stimuli can be seen 25-35 minutes after stimulation (Gunnar, 1992).

Infants cried more in response to circumcision or a heel lance than being weighed or examined, but all groups had comparable rises in cortisol levels (Gunnar, et al., 1988). Infants subjected to unanesthetized circumcision demonstrated a decreased amount of crying when given a pacifier to suck, but the groups had comparable increases in serum cortisol levels, regardless of amount of crying (Gunnar, et al., 1984; Gunnar, et al., 1981). Change in cortisol was sensitive to and influenced by type of surgical technique (Gunnar, et al., 1984) and to skill level of the physician performing the procedure (Gunnar, Malone, & Fisch, 1985). Higher elevations in cortisol levels were also associated with increased arousal post procedure (Gunnar, et al., 1984; Gunnar, Malone, & Fisch, 1985).

Further study by Gunnar and colleagues replicated her previous findings and showed the ability of optimally healthy newborns to differentially respond to qualitatively different stressors. The salivary cortisol increase seen with handling stress habituated when a discharge examination was repeated. Newborns in the heelstick group showed similar increases in cortisol when the stimulus was repeated (Gunnar, et al., 1992).

In considering the seeming contradiction of decreased crying in infants but similar rises in cortisol in response to stressors, one possible conclusion is that behavioral distress may not accurately reflect the meaning of the experience to that individual. Therefore, in addition to behavioral measures, physiologic measures are indicated for assessment of pain in non-verbal individuals. Further investigation of this issue strengthens the argument for both pre-emptive pain management and providing pain relief for known painful

procedures. In contrast to the reduced pain behaviors but rise in cortisol seen in response to pacification during painful stimuli, it was found that administration of analgesia reduced both behavioral distress and significantly decreased the rise in cortisol (Stang, Gunnar, Snellman, Condon, & Kestenbaum, 1988).

Many of the above studies employed serum cortisol levels. Since the initial studies were performed, technology has advanced so that cortisol levels are able to be obtained non-invasively using saliva. Use of salivary cortisol avoids exposing subjects to additional invasive procedures such as heelstick or venipuncture. There is a high correlation between plasma and salivary cortisol levels (Francis, et al., 1987; Gunnar, Connors, & Isensee, 1989; Kirschbaum & Hellhammer, 1989).

Pain has been discussed as a subjective multidimensional experience. Given this, the three measures discussed - cry, vagal tone, and cortisol, should complement each other in an attempt to obtain an accurate and valid indication of the pain an infant is experiencing during an acute pain inducing procedure.

Pain Management in Infants

It is only within the past two decades that the medical community has recognized that infants experience pain. This, coupled with the fear of side effects from pharmacologic agents and ethical constraints concerning subjecting infants to experimental pain, has resulted in a haphazard and often ineffective approach to pain management in infants. Generally interventions can be classified as pharmacologic or non-pharmacologic.

Pharmacologic intervention carries with it the risk of side effects and the risk-benefit ratio must be considered. Prescription of medications is not under the domain of

staff nurses, though nurses can impact efficacy of pain management by considering administration schedule and advocating for the patient when pain relief is insufficient or is not achieved.

Nursing has primary responsibility for non-pharmacologic methods of pain relief. Non-pharmacologic interventions include, among others, positioning, music, environmental manipulation, swaddling, parental presence, the use of sucrose, facilitating hand-to-mouth behaviors, and sucking (Greenberg, in press). Some of these interventions have been implemented based on the thought that they might be effective; others have been studied, although the studies have often not been replicated.

Sucking

Pacifiers are commonly used to reduce pain induced vocalizations. The relationship of sucking as a comfort measure to alleviate distress caused by painful stimuli has been studied. Field and Goldson (1984) suggested that nonnutritive sucking during heelsticks may attenuate signs of behavioral distress in both preterm and term neonates. Miller and Anderson (1993) found that nonnutritive sucking during invasive procedures in sick infants contributed to physiological adaptation. Campos (1989) studied 2-week and 2-month-old infants undergoing heelsticks and injections respectively. She found that both comfort measures of swaddling and pacifier use soothed infants subjected to painful stimuli, as measured by cry and heart rate, but they differed in effectiveness. Pacifier use showed a more rapid onset of soothing, but infants had a rebound in arousal when the pacifier was removed after the three minute post-intervention period. This rebound might not occur with a longer period of pacification. Swaddling was not as immediately

effective in decreasing cry and heart rate, but did produce a reduction in arousal, especially with two month olds and was less likely to rebound upon termination. There was a slight positive trend toward increased sleep in swaddled infants over pacified infants.

Nonnutritive sucking helps an infant organize behaviors, adapt to stimuli (Kimble, 1992; Pickler & Frankel, 1995) and may increase the release of pain-alleviating neurotransmitters, thus aiding in stress reduction (Field, 1993). Therefore, nonnutritive sucking may augment other interventions aimed at pain alleviation and provide the benefit of stress reduction. If sucrose is to be administered via a pacifier, then the effects of sucking alone must be examined in order to evaluate the effectiveness of sucrose as a pain alleviating intervention.

Sucrose

Sucrose is thought to be mediated through the opioid pathways, thus having the potential of pain reduction or alleviation. Blass et al. (1987) demonstrated elevated paw lift latencies in rat pups and decreased distress vocalizations after intraoral infusion of sucrose. Both of these were reversible with administration of an opioid antagonist. This suggests that the changes in perception of pain and distress are modulated by endogenous opioids.

Blass et al. (1989) used sucrose when studying hand-mouth coordination in human infants; they did not inflict a pain stimulus. Infants showed increased calming immediately after oral administration of 12% sucrose solutions over water that persisted beyond termination of sucrose administration (Blass, et al., 1989). When the calming effects of sucrose were studied, again, no pain stimulus was used; varying amounts, to as little as 0.2

ml of a 14% sucrose solution reduced crying compared to water or sucking on a pacifier (Smith, et al., 1990). Crying was eliminated in almost all infants within two minutes of sucrose administration. When a pacifier was used to administer either water or sucrose, sucrose calmed more effectively. This calm was sustained after pacifier removal in infants who received sucrose, while most infants who received water via pacifier resumed baseline rates of crying after pacifier removal. This suggests that calming from orogustatory and orotactile stimulation operate through differing pathways (Smith, et al., 1990).

The antinociceptive properties of sucrose administered via syringe were examined in infants undergoing heel lance. Infants who received 12% sucrose demonstrated reduced crying in response to the procedure relative to infants who received water (Blass & Hoffmeyer, 1991). The antinociceptive effects of sucrose had a short latency. The same article discussed like findings for infants undergoing circumcision. Water via pacifier reduced crying over control infants, but crying was even further reduced when sucrose was administered via pacifier (Blass & Hoffmeyer, 1991). The authors offered sucrose as a potent, yet benign intervention for use in alleviating stress and pain in infants. Preterm infants who received 2 cc of a 50% sucrose solution prior to heel lance also demonstrated shorter cry times and less increase in heart rate than when they received a water placebo prior to heel lance (Bucher, et al., 1995).

The analgesic effect of intraoral sucrose was studied in 8 - 11 year old children using the cold pressor test as the pain stimulus. The cold pressor test is an experimental pain paradigm in which the subject immerses the forearm in cold water. Children were able to hold their arm in the water for significantly longer periods while holding 24%

sucrose in their mouth, although there was no effect detected on tolerance or intensity ratings (Miller, et al., 1994). This indicates that sucrose may also have analgesic effects in older children, although more research is needed.

Other research questions the antinociceptive effectiveness of sucrose. The effectiveness of 12% sucrose during immunization administration was studied in older infants, 2 weeks to 18 months. Given orally, in the absence of nonnutritive sucking, sucrose did not significantly reduce crying over sterile water, although both did significantly reduce crying over infants who received no intervention and only one injection (Allen, et al., 1996). When duration of crying was evaluated in newborns undergoing heel lance who were given a 7.5% sucrose solution versus sterile water, no difference in crying was found (Rushforth & Levene, 1993). Level of arousal at time of heel lance was correlated with duration of crying, with more awake babies crying for longer periods of time (Rushforth & Levene, 1993). Haouari et al. (1995) evaluated the analgesic efficacy of 50%, 25%, and 12.5% oral sucrose solutions and a control of sterile water during heel lance in newborns. They found that 50% sucrose significantly reduced cry time and heart rate. This was statistically significant in the first minute after heel lance in the 50% sucrose group and reduction in duration of cry became significant in the 25% sucrose group at 2 minutes post procedure (Haouari, et al., 1995). The 12.5% concentration of sucrose solution was not statistically significant from the sterile water group, but overall there was a trend to reduction in crying times with increasing concentration of sucrose solution (Haouari, et al., 1995).

These studies indicate that the analgesic efficacy of sucrose may be a function of solution strength, possibly related to the presence of nonnutritive sucking. Sucrose concentrations of 7.5% appear to have a pain alleviating effect similar to water, which is better than controls but not statistically significant. Concentrations of 12% may reduce pain manifestations, but as sucrose concentration increases, pain manifestations decrease.

Relationship to the Proposed Study

The Gate Control Theory provides the framework upon which this study is based. It explains the effectiveness of both sucrose and sucking since transmission of pain impulses can be modulated by opioid and nonopioid mechanisms. Aδ and C fibers transmit the majority of the nociceptive stimuli through the dorsal horn of the spinal cord. In the dorsal horn, nociception can be affected by impulse transmission through Aα fibers as well as descending inhibition from the thalamus.

The dorsal horn has a particularly dense concentration of opioid receptor sites. Opioids produce analgesia by preventing pain impulse transmission. Opioid agonists bind to receptor sites which reduces neurotransmitter release (Yaster & Maxwell, 1993), reducing ability to propagate the pain impulse. Evidence suggests that sucrose is mediated through the opioid pathways since its analgesic properties are fully reversed when an opioid antagonist is administered. Sucrose, mediated through the opioid pathways, occupies the pain impulse receptors, thus blocking pain signal transmission. If sucrose is given prior to painful stimuli, it occupies the receptor site, once again closing the gate to transmission of the nociceptive impulse.

Sucking on a pacifier may inhibit transmission of nociceptive stimuli by increasing Aα fiber impulse transmission, sending signals to the dorsal horn faster than the pain fibers. This closes the gate on those pain impulses, reducing Aδ and C fiber transmission of these signals to the higher perceiving centers in the brain. It has also been hypothesized that sucking increases release of pain alleviating neurotransmitters (Field, 1993). There is little research to support this which, while plausible, needs to be substantiated.

Summary

Pain has been discussed as a subjective multidimensional experience. Given this, the one behavioral and two physiologic measures discussed - cry, vagal tone, and cortisol - were used in an attempt to obtain an accurate and valid indication of the pain an infant experiences during the stress of heelstick, an acute pain inducing procedure.

Interventions must be implemented when an infant is experiencing pain. The efficacy of pharmacologic interventions has been validated for moderate to severe pain (Yaster & Maxwell, 1993; Yaster, Tobin, & Maxwell, 1993). Infants experiencing mild to moderate pain often are not treated. This may be due to insufficient knowledge regarding appropriate management; the opinion that the risks of treatment outweigh the benefits; or caretakers' biases such as "they can tolerate it" or "the pain will only last a short time". Nurse's often implement non-pharmacologic "comfort" measures. There have been relatively few studies that validate the efficacy of these measures for pain relief (Carlson, 1996). Some interventions have been studied, such as music therapy (Collins & Kuck, 1991), but there have been no replication studies. Sucking has been studied repeatedly (Campos, 1989; Field & Goldson, 1984; Gunnar, et al., 1984; Miller & Anderson, 1993).

Sucking may attenuate pain behaviors, and even positively impact the pain experience to an extent, but it probably does not alleviate pain.

The efficacy of 12% sucrose solution or greater as an analgesic in infants has shown promising results (Blass & Hoffmeyer, 1991; Bucher, et al., 1995; Haouari, et al., 1996). The research from this study adds to the research regarding the efficacy of sucrose as an analgesic in neonates. This research utilized more sophisticated measures of heart rate response to pain in infants than the previous studies, thus providing a more precise assessment of the elusive concept of pain in infants. This study also evaluated a different method of administering the sucrose than other studies, a pacifier coated with granulated sugar. This method of administration is more readily available to the clinician, which should contribute to higher rates of implementation.

The quality improving, cost cutting health care environment of today demands an effective nursing practice. In order to meet this demand, nursing practice must include research based interventions. Based on the Gate Control Theory, sucrose and sucking may both possess pain alleviating properties on their own. When used together, they may also act synergistically to have an additive effect in pain reduction. Both hypothesis were evaluated in this study. The results from this study add to the paucity of knowledge regarding non-pharmacologic pain interventions in infants.

CHAPTER 3: Methodology

Research Design

The purpose of this study was to evaluate the efficacy of sucrose, administered via a coated pacifier, in reducing pain behaviors compared to sucrose solution delivered via syringe, a water moistened pacifier, and no intervention. A randomized, complete block experimental design was used. The complete block design was implemented so that each successive group of 4 infants was randomized to treatment group; e.g. the first 4 infants were randomized, one to each treatment group, then the next 4 infants were randomly assigned to each of the 4 treatment groups, and so on until all 84 infants had been assigned to treatment group. This was done in an effort to eliminate the potential effect of experience with the experimental protocol affecting infant response if the first 21 infants were given one treatment, the next 21 given another treatment, and so on.

There was one independent variable with four levels and three dependent variables. The levels of the independent variable were the treatment group assignments:

1) sucking on a water moistened pacifier,
2) sucking on a sucrose (table sugar) coated pacifier,
3) sucrose solution via syringe prior to heelstick with no pacifier, and
4) no intervention.

The dependent variables were three measures used to assess the pain experience in infants: duration of cry, vagal tone, and salivary cortisol.

Selection of Subjects

A purposeful sample was obtained in that parents of all subjects who fit inclusion criteria were asked for consent to participate until the needed sample size was obtained. A total of 192 parents were approached for consent, 84 (44%) gave consent to include their infant in the study, 108 (56%) denied consent. There was random assignment to groups as previously described.

Inclusion criteria for infants included parental consent, a birth weight between 2500 - 4000 grams, age of birth to 72 hours, APGAR scores of at least 7 at one and five minutes of age, estimated gestation of at least 37 weeks, and no known congenital anomalies. Maternal exclusion criteria included history of substance abuse and chronic or infectious disease processes during pregnancy.

Infants undergoing the painful procedure of heelstick as part of a routine blood sample collection for newborn metabolic screening, who met selection criteria, and whose parents gave informed consent were included in a purposeful sample (see Appendices A and B for consent forms). Subjects were selected infants delivered in a moderate sized hospital in Southern California, that performs 180-200 deliveries/month. Because the immediate postpartum period is a vulnerable period for families, a brief overview of this study, that participation was voluntary, and that parents might be approached for consent to participate after their child was born was presented during the childbirth education classes the hospital offers prior to delivery of the baby. Data collection was done in a

separate room in the LDRP (labor delivery recovery postpartum) unit equipped with a cardiac monitor.

Sample Size

A power analysis was performed to determine sample size. An effect size of 1.088 for cry was determined from a similar study looking at the efficacy of sucrose for pain alleviation in infants (Blass & Hoffmeyer, 1991). To achieve a power of .8 with an effect size of 1.088 and an alpha of .05, 20 infants would need to be studied (Borenstein & Cohen, 1988). Given that 1.088 is an extremely large effect size and that it was difficult to determine effect size of the other dependent variables from the literature at the time of calculation, but postulating that this large of an effect size would be unlikely to be observed in the other dependent variables, it was decided to increase sample size in order to discern detectable differences. Positing an effect size of .38 (which is slightly less than the .40 that Cohen (1988) uses to define a large effect size) and an alpha of .05, studying a total of 80 infants achieves a power of .80. A total of 84 infants were studied, 21 per treatment level, to account for the potential of missing data in some subjects.

Instrumentation

Pain assessment in infants is imprecise, with no widely accepted existing tool. The subjective rating of the pain experience by the individual experiencing pain has been the accepted standard of pain assessment. Due to the inherent difficulties that arise when assessing non-verbal populations, there are no measures presently in existence that have demonstrated reliability and validity as to being precise measures of pain in infants. The question arises: is it pain or stress that is being measured? Nociceptive stimuli evoke a

more general stress response. Reaction to painful stimuli is variable and dependent on many things such as: individual characteristics, infant state, and pain condition e.g. acute versus chronic. Multidimensional assessments have greater potential for accuracy than single measures. With these considerations, three measures were chosen as measures of stress in infants, the first two having theoretical legitimacy as being specific to pain: duration of cry, vagal tone reactivity, and salivary cortisol reactivity.

Duration of Cry

Given the wide acceptance of crying having face validity as an indicator of pain in infants, presence of crying in response to a nociceptive stimuli was used as a measure of pain. The data collection period was videotaped with audio on a Sony CCD-TR83 camcorder.

Sucking may decrease observed pain behaviors, but this may not be a reliable indication of the amount of pain being experienced. Therefore, two physiological measures were also monitored.

Vagal Tone

Vagal tone has been reported as a promising index of pain in infants that responds quickly to nociceptive stimuli and rapidly returns to near baseline after termination of the stimuli (Porter, et al., 1988). Vagal tone was measured by continuous 3-lead electrocardiograph (ECG) recording via a Hewlett-Packard 78532 ECG recorder down-loaded to computer via the one volt ECG output port connector. ECG data were down-loaded to a 486DX-100 MHZ portable computer equipped with a Keithley Metrabyte DAS-16 analog digital interface board (A to D board) to digitize the analogue ECG signal

for reading by the computer. The data, as R to R intervals of the ECG, to the nearest millisecond, were stored on disk (Vgtone computer software program developed by R. Powers M.D. & L. Franck, PhD, RN) for later quantification.

MXedit software (Delta-Biometrics, Bethesda, MD) was used to visually display heart period data, edit outliers due to artifact, and to calculate the amplitude of respiratory sinus arrhythmia using the vagal tone index (Porges, 1985). Artifact correction was done by noting aberrant values on visual inspection of R-R intervals, then using integer addition and division of sequential R-intervals to approximate the preceding and succeeding R-intervals. MXedit uses a time series analysis to estimate RSA per epoch. MXedit uses a detrending algorithm (a moving polynomial filter and bandpass) to remove aperiodic trends and periodic heart patterns that are outside of the respiratory frequency band. The heart period data were sampled in 250-ms intervals using a 21-point moving cubic polynomial to detrend data and a 25-point symmetrical bandpass filter applied to pass variance between a 0.3-Hz and 1.3-Hz range (e.g. range of spontaneous breathing for infants that occurs at 20 - 80 breaths per minute). Scores on the vagal tone index reflect the natural logarithm of the variance within the 0.3 - 1.3-Hz frequency band and are expressed in natural logarithm units per millisecond squared (ln/ms^2). Vagal tone index was calculated on sequential 30-second epochs, and the mean of the epoch was used in data analysis.

Cortisol

An infant responds to the stress of pain by secreting, among others, adrenocortical hormones (Anand & Hickey, 1987). Cortisol is an adrenocortical hormone that has been

used to measure an infant's response to pain (Gunnar, et al., 1981; Gunnar, et al., 1984; Gunnar, Malone, Vance, & Fisch, 1985; Talbert, Kraybill, & Potter, 1976). Cortisol can be measured from saliva.

Saliva sample collection. Issues of saliva sample collection, storage, and analysis were addressed to ensure accuracy of data and subsequent interpretation. Salivary cortisol elevations in response to stimuli can be seen at 25-35 minutes after stimulation (Gunnar, 1992). Therefore salivary cortisol for baseline level was collected at the start of the study and the post-procedure sample was collected 25 minutes after the heelstick.

Flow of saliva may need to be stimulated by application of a small amount of citric acid put on the tongue (Kirschbaum & Hellhammer, 1989). Infants were given a pledget to suck on for one minute, if an adequate amount of saliva was not obtained, 1 - 2 drops of a 10% citric acid solution was administered. Then the dental pledget was placed in the infant's mouth and the infant encouraged to suck on it.

Cortisol in saliva is relatively stable. When samples were stored at ambient temperatures, cortisol concentrations were unaltered for up to 30 days (Kirschbaum & Hellhammer, 1989). This assumes particular importance for ease of sample collection when subjects are collecting samples at home. When samples are stored in the laboratory, they should be kept at -20 degrees Centigrade (Gunnar, 1992). This enables enough samples to be collected and analyzed in the same batch to control for variation between assays.

All saliva samples from a subject should be assayed in the same assay batch in order to control for problems with interassay variation. When different treatments are

being compared, in order to avoid interpreting batch differences as treatment effects, it is best to counterbalance samples across assay batches (Gunnar, 1992).

Saliva samples collected for this study were immediately frozen after collection and stored at -20° C until shipped over night delivery on dry-ice to the Behavioral Endocrinology Laboratory (BEL) at Pennsylvania State University, University Park, PA. At the BEL, samples were stored frozen at -80° C until assayed for cortisol.

Saliva sample analysis for cortisol. Analysis was done using a modification of a coated tube radioimmune assay for use with serum (Diagnostic Products Corporation, Los Angeles, CA). The assay was conducted following the manufacturer's recommended modification for use of the serum kit with saliva. Before testing, samples were pH corrected into the 6-8 range using 20x phosphate buffered saline (Schwartz & Granger, 1997). Samples were tested in duplicate and the average intra-assay coefficient of variation was less than 3%. Both samples from each infant were tested in the same batch. To reduce variation between batches all samples were tested using reagents from the same lot in 3 assay batches. Inter-assay reliability was estimated across the 3 batches using external controls (BioRad, Anaheim, CA) representing cortisol values in the high (1.32 ug/dl), mid (.62), and low (.10) range. Inter-assay coefficients of variation were 1.48%, 3.08%, and 6.86% for the high-, mid-, and low-range respectively. The cortisol scores used in the data analyses were averaged across duplicate tests and are expressed in ug/dl.

Data Collection and Recording

Demographics. In order to look for the effect, or covariation, of extraneous variables on the results obtained, certain demographic data were collected. These

included: gender, ethnicity, type of delivery (vaginal or Cesarean), delivery anesthetic, administration of narcotics and length of time administered prior to delivery, infant's age in hours, time since last feed in minutes, history of circumcision, exposure to previous heelsticks, number of times heel was lanced during data collection, and length of time, in seconds, that it took to perform the heelstick and blood collection (refer to Appendix B for Data Collection Sheet). Gender (Owens & Todt, 1984) and age may influence how the infant responds to pain (Owens, 1984). Previous heelsticks may influence the infant's response to subsequent injury by making them hypersensitive (Fitzgerald, Millard, & McIntosh, 1989).

Study personnel. The principle investigator collected all data in this study. The same phlebotomist performed all the heelsticks and blood specimen collection in order to standardize the stimulus as much as possible.

Data Collection Protocol

Infants were brought to a quiet alert state, awake with open eyes, responding to the environment with quiet or active movement and not crying at the beginning of data collection.

The study phases of intervention, heelstick and blood collection, and three-minutes post blood collection were videotaped with audio beginning at three minutes prior to heelstick until three minutes after pressure was released from the heel. ECG data were recorded via heart rate monitor in contiguous segments starting shortly after baseline salivary cortisol collection until just prior to post-heelstick salivary cortisol collection.

The sequence of experiment phases was: 1) collection of pre-procedure sample for salivary cortisol; 2) ten-minute baseline vagal tone data collection; 3) two-minute intervention period as randomly assigned, the two interventions involving pacifiers continued throughout phases 4 and 5; 4) procedure when the heel was picked up, swabbed, lanced, blood collected, and pressure held with gauze until bleeding stopped and a Band-aid is applied; 5) three minute post-procedure data collection period for duration of cry; if the child cried for a longer period, videotaping was continued until the child stopped; and 6) post-procedure salivary cortisol obtained 25 minutes after heelstick and blood collection was completed (see Appendix C for detailed Experimental Protocol).

Data Processing

This study generated interval data. There was one independent variable, treatment group, having four levels and three dependent variables: duration of cry, vagal tone reactivity, and salivary cortisol reactivity.

Duration of Cry

Duration of cry was calculated as total time crying, measured in seconds, during the heelstick and blood collection procedure and 3 minutes post-procedure time; if the child cried for a longer period of time measurement continued until the child stopped crying.

The heelstick and blood collection were videotaped with time in seconds superimposed on the picture. The tape of each infant was viewed by the principle investigator to calculate duration of cry vocalizations, in seconds, during and after the heelstick. To verify accuracy of calculation of duration of cry, a nurse with 14 years of

pediatric / neonatal experience reviewed 21 videotapes (25% of the sample). Pearson correlation was calculated to determine inter-rater reliability between both raters on the 21 ratings. Correlation between the 2 raters was essentially perfect at 99.98%.

The Levene statistic was calculated to test for the homogeneity of variances for duration of cry. For the raw cry score the Levene statistic was 4.184 (significant at .008), indicating that the assumption of equal variances of the treatment groups was violated. To correct for this, a square root transformation of raw cry scores was done and the Levene statistic recalculated after the transformation. This was not significant, supporting the assumption of equality of variance across all treatment groups. The square root transformation was used in all statistical analysis of the cry score data.

Vagal Tone

The heart rate data files were edited prior to calculation of the vagal tone index by two research assistants, experienced in the use of MXedit. To assure congruence of editing decisions between the two raters when correcting for artifact, a random cross section of 40% of the sample (34 infant's files) were edited by both research assistants with agreement reached on the editing decisions. If questions arose about editing decisions when a research assistant was editing alone, consultation was done with the other to reach a decision.

MXedit calculates a vagal tone index value based on 30 second data epochs. Some time is lost due to the initial calculation of interbeat variance. Therefore, each 5 minute segment of heart rate data yielded an average of 9 vagal tone index values. The mean of these values was used as the vagal tone index for that data collection period.

Pearson correlation indicated that the first two 5 minute vagal tone values were highly correlated ($r = 0.78$) so the average of the 2 was used as the vagal tone baseline value for the infant.

A simple change score (baseline minus heelstick procedure) was calculated for vagal tone and used in statistical analysis. Further evaluation of quantitative analysis techniques of cardiovascular measures indicated that, because a degree of correlation usually exists between baseline measure and change score, the degree of change should not be considered "pure" or independent of baseline (Manuck, Kasprowicz, & Muldoon, 1990). A simple difference score, which is often significantly and positively associated with the baseline value, may not adequately control for the influence of the baseline measure. Analysis of covariance (ANCOVA) on posttest values, with the baseline (pre-test) value treated as the covariate, can help factor out the influence of the pre-test value in order to evaluate treatment effects between groups (Burckhardt, Goodwin, & Prescott, 1982). Because multiple dependent variables were used, MANCOVA was used to evaluate group differences with the heelstick procedure vagal tone index used in the analysis and vagal tone baseline used as a covariate.

Cortisol

Because resting cortisol values may influence the magnitude of post-heelstick response (see above discussion under vagal tone), MANCOVA were used to analyze group differences with post-heelstick cortisol used in the analysis and pre-heelstick cortisol used as a covariate. Group differences using simple change scores (post-heelstick minus value pre-heelstick) were also examined using MANOVA.

Data Analysis

Data were analyzed using SPSS statistical software package (version 7.5, SPSS, Chicago, IL). There were no missing data. Descriptive statistics were completed to summarize sample characteristics.

Statistical Analysis

Multivariate analysis of variance (MANOVA) were used to examine differences between the four treatment groups for the three dependant variables (cry, vagal tone, salivary cortisol) to determine if these differences supported the study hypotheses.

MANOVA were run using the square root transformation of duration of cry, vagal tone index during blood collection procedure, and post-heelstick salivary cortisol level. To control for the influence of baseline value on vagal tone and cortisol response, multivariate analysis of covariance (MANCOVA) were analyzed using baseline vagal tone and pre-heelstick salivary cortisol level as covariates.

MANOVA were also run examining the vagal tone change score (baseline minus heelstick procedure values) and salivary cortisol change score (post-heelstick minus pre-heelstick value).

When differences among the group means were significant, post hoc multiple comparison tests were performed to determine which groups showed significant differences. Increasing the number of comparisons increases the probability that significant findings are due to chance and increases the likelihood of a Type I error. To compensate for this the Bonferroni *t* statistics, based on Student's *t* statistic, approach was used. Using Bonferroni *t* statistics, the alpha level of the individual comparisons is

reduced by dividing the individual alpha levels by the number of comparisons (Pedhazur & Schmelkin, 1991). When comparing a small number of pairs of means, as in this study, Bonferroni is more powerful than Tukey's HSD (honestly significant differences) (SPSS, 1997). For completeness in evaluating the data, results from other post hoc tests were evaluated and revealed comparable results.

Pearson Chi-Square was used to detect group differences due to type of anesthesia, type of delivery, administration of intravenous narcotics prior to delivery, gender, ethnicity, history of circumcision, or history of previous heelstick. Analysis of covariance (ANCOVA) was used to analyze any group effect or covariation, of age, weight, time since last feeding, heelstick and blood collection procedure length, gestational age. Correlations between the variables were evaluated using Pearson Product-Moment correlations.

As a separate sub-question, vagal tone response post-heelstick was examined in order to determine the effect of treatment on recovery. Repeated measures ANOVA were used to analyze vagal tone raw scores. This question was not directly related to the study hypotheses but was exploratory and adds to the body of literature regarding vagal tone response to pain in infants.

Assumptions of the Study

There were three basic assumptions of this study. The first was that infants are capable of experiencing pain, regardless of their inability to verbalize or communicate the pain experience. The second was that the pain experience is subjective and thus individualized. Infants may perceive and respond to the same stimuli in different ways.

The third assumption was that the measurement methods used are indicative of pain in infants. For this study, it was accepted that an awake infant who was not crying previous to infliction of the nociceptive stimulus and who started crying was reacting to the painful event (Allen, et al., 1996; Bucher, et al., 1995). Changes in vagal tone (Gunnar, et al., 1995; Porter, 1993) and salivary cortisol values (Gunnar, 1992; Gunnar, et al., 1995) were also attributed to reaction to a painful stimulus in infants who were awake and presumably experiencing no pain during baseline data collection.

Ethical Considerations

While it is unethical to subject infants to unnecessary painful events, all infants have blood collected via a heelstick for state mandated newborn metabolic screening. Therefore, the infants in this study were not subjected to any additional painful procedure and, because of the interventions, may even have benefitted by pain reduction if the interventions were efficacious. A heelstick is not generally considered a major or extremely painful procedure by the health care team. Because of this, pain relief interventions are not routinely implemented when infants are undergoing the procedure. Randomizing infants to control or intervention groups was not considered unethical since treatment was not being withheld.

Human subjects approval was obtained from the University of San Diego Committee on the Protection of Human Subjects (Appendix D). Approval was also obtained from the Institutional Review Board of Saddleback Memorial Medical Center, the data collection site (Appendix E).

Patient confidentiality was maintained. All subjects were assigned a study number that identified all collected data. The consent form, which identified subject name with number, was kept separate in a file cabinet in the investigator's home.

Parents of all infants who met inclusion criteria and were available on data collection days were approached for consent. Parents were assured anonymity and that the mother's care or care of her infant would not be influenced by participation, or nonparticipation, in the study. Parents were told that their baby would be assigned to one of four experimental groups by random assignment and that none of the treatments was considered harmful or standard, e.g. a pacifier is not always given to an infant to comfort during heelstick. Parents were told they could withdraw their infant from the study at any time without consequence. All costs incurred by participation in the study (pre and post heelstick salivary cortisol levels, electrocardiograph recordings, audiotapes) were assumed by the investigator. Charges for the state-mandated newborn metabolic screening were the responsibility of the parents.

If the investigator believed that the infant was being overly stressed in the post heelstick data collection period, data collection would have been stopped. The infant would have been swaddled, held, rocked, offered a pacifier, or otherwise comforted. No infants were excluded from the study because of excessive distress after heelstick . The majority of infants fell asleep shortly after the blanket was wrapped back around them. One infant produced cry vocalizations for a lengthy period of time (565 seconds), but the intensity and frequency continued to decrease over the period of time so it appeared that the infant was self-consoling. Another infant, whose mother had consented to include the

infant in the study, was excluded from the study, per father's request, after the pre-cortisol sample was obtained.

CHAPTER 4: Analysis and Evaluation of Findings

As hypothesized, infants offered the sugar coated pacifier demonstrated the fewest pain behaviors associated with the painful procedure of heelstick. The group offered no intervention demonstrated the greatest amount of pain behaviors. The single intervention groups, water moistened pacifier and oral sucrose solution, demonstrated mid-range pain behaviors between the sugar coated pacifier and control groups, although not statistically different from the other two groups.

Demographics of the sample and characteristics of the dependent variables will be examined in this chapter followed by the results of hypothesis testing and the effect of treatment on vagal tone response over time. The influence of demographic characteristics on the dependent variables and discussion of findings will also be presented

Description of Sample

Demographic Data

All data were collected at one institution in Southern California whose patient population is predominantly middle to upper-middle class. Selection criteria were formulated to capture a homogenous population of healthy term infants. See Appendix F for description of demographic characteristics of the total sample and by group. There were no significant differences in group characteristics.

Ethnicity of the sample was fairly representative of the patient population of the institution where data were collected. Infants in the sample included 73.8% Caucasian, 10.7% Hispanic, 4.8% Black, and 10.7% other (Asian, Filipino, Caucasian/Hispanic, Caucasian/Black, Caucasian/Asian).

Infants must be at least 12 hours of age before blood can be drawn for the newborn metabolic testing that was the noxious stimuli. The age range for infants in this study was 12 to 32 hours, with a mean of 18.99 (SD 5.59). Infants weighed between 2655 - 3990 grams, mean 3412 grams (SD 309.78). The mean gestational age of infants was 39.34 weeks (SD .8836), range 37.28 - 41 weeks.

The time since the infant had last fed ranged from 10 to 320 minutes, mean 68 minutes (SD 59.55). The range for length of the heelstick procedure was 88 - 315 seconds, mean 155 seconds (SD 46.57). Five (6%) of the infants had been subjected previously to the painful stimuli of heelstick, and 79 (94%) had not been subjected to heelstick prior to having blood drawn during the study.

Nine male infants were circumcised prior to data collection. Time since circumcision ranged from 5 to 330 minutes, mean 86 minutes.

Dependent Variables

Cry. The range for duration of cry for the sample was 0 to 565 seconds, with a mean of 97 seconds (see Table 1). Evaluation of the Levene test of homogeneity for cry indicated that homogeneity of the sample was skewed. A square root transformation was done to correct for this. Subsequent evaluation by the Levene test indicated acceptable homogeneity. Therefore, transformed cry scores were used for data analysis.

Table 1

Duration of Cry Characteristics

Duration of cry in seconds	Water Pacifier	Sugar Pacifier	Oral Sucrose	No Intervention	Total Sample
minimum	7	0	2	13	0
maximum	565	200	162	334	565
mean	126	46	85	133	97
SD	136.93	55.93	47.96	93.53	95.75

Vagal tone. Vagal tone index (VTI) at baseline ranged from .80 to 5.52 ln/ms^2, mean 3.0207 (see Table 2). VTI during heelstick procedure ranged from .44 to 4.47 ln/ms^2, mean 2.3633. Vagal tone change score was highly correlated with baseline ($r = .623$, $p < .01$).

Cortisol. Pre-heelstick cortisol levels for the sample ranged from .133 to 5.804 μg/dl, mean .90475 (see Table 3). Post-heelstick cortisol levels ranged from .108 to 6.878 μg/dl, mean 1.04734. The cortisol change score was highly negatively correlated with pre-heelstick cortisol level ($r = -.460$, $p < .01$), the lower the baseline cortisol the greater the magnitude of change in cortisol level. Conversely, the higher the baseline cortisol, the lower the magnitude of post heelstick change in cortisol level.

Results of Hypotheses Testing

Prior to testing the hypotheses, the assumptions underlying MANOVA were tested and met.

Table 2

Vagal Tone Index Means during Specific Epochs

VTI in ln/ms^2	Water Pacifier	Sugar Pacifier	Oral Sucrose	No Intervention	Total Sample
Baseline					
mean	2.9857	2.7079	3.1721	3.2171	3.0207
SD	.8399	.9045	.8620	1.1826	.9612
Intervention					
mean	2.6752	2.2276	2.6586	3.0971	2.2665
SD	.8696	1.0316	.8029	.9837	.9607
Procedure					
mean	2.3648	1.8695	2.5805	2.6386	2.3633
SD	.7615	.7411	.7626	.7425	.7987
Change score					
mean	.6210	.8383	.5917	.5786	.6574
SD	.7221	1.0295	.6442	1.0466	.8696

Table 3

Cortisol Level Means

Cortisol in μg/dl	Water Pacifier	Sugar Pacifier	Oral Sucrose	No Intervention	Total Sample
Pre-procedure					
mean	.85876	.96276	.73062	1.06686	.90475
SD	.87747	.72031	.87634	1.32420	.96636
Post-procedure					
mean	.83410	.95133	1.08267	1.32126	1.04734
SD	.66810	.61795	.91345	1.59254	1.02220
Change score					
mean	.0247	.0114	.3520	.2544	.1426
SD	.6438	.8550	1.2559	1.1437	.9993

Homogeneity of groups. ANOVA was used to evaluate group differences in baseline values. No significant group differences were detected for vagal tone at baseline (F (3, 80) = 1.227, p = .305) and pre-heelstick cortisol (F (3, 80) = .456, p = .714).

To strengthen the study design by controlling for variability due to familiarity with the study protocol, it was set up as a randomized complete block design. ANOVA was used to evaluate the effect of the randomized complete block design for the dependent variable of square root of cry on group differences. No significant blocking effect was found (F (20, 60) = .870, p = .623). Therefore, no manipulation was done to control for the effect of the blocking procedure.

Correlation of dependent variables. Pearson correlation demonstrated that the square root transformation of cry and vagal tone index at heelstick procedure were correlated (r = .259, p = .018).

Primary Hypothesis

The major hypothesis evaluated in this study was:

- infants offered a sucrose coated pacifier demonstrate decreased pain responses (shorter duration of crying, smaller decrease in vagal tone, smaller elevation in cortisol level) when undergoing painful procedures compared to infants undergoing painful procedures who are offered sucrose solution via a syringe, a water moistened pacifier, or no intervention.

MANOVA demonstrated significant group differences when cry, vagal tone at heelstick procedure, and post-heelstick cortisol were examined (see Table 4). Statistically significant group differences were demonstrated for duration of cry (F (3, 80) = 6.275, p =

Table 4

MANOVA of Cry, Vagal Tone, and Cortisol

Source	Dependent Variable	df	Mean Square	F	Sig.
Group	Square root of cry	3	115.302	6.275	.001
	Vagal tone at heelstick	3	2.567	4.540	.005
	Post-heelstick cortisol	3	.917	.873	.459

.001) and vagal tone at heelstick procedure ($F(3, 80) = 4.540$, $p = .005$). No statistically significant group differences were demonstrated for cortisol (Figure 2).

Post hoc contrasts using the Bonferroni test for multiple comparisons revealed a statistically significant:

- shorter duration of cry for the sugar coated pacifier group compared to the control group (mean difference = -5.3419, $p = .001$) and compared to the water-moistened pacifier group (mean difference = -4.4872, $p = .006$) (Figure 3), and
- lower vagal tone during heelstick for the sugar coated pacifier group as compared to the control group (mean difference = -.7690, $p = .008$) and between the sugar coated pacifier group and the oral sucrose solution group (mean difference = -.7110, $p = .018$).

To control for the influence of baseline value on vagal tone and cortisol, MANCOVA was run using cry, vagal tone at heelstick procedure, and post-heelstick cortisol as the dependent variables, and vagal tone at baseline and pre-heelstick cortisol as covariates. MANCOVA demonstrated main effects similar to MANOVA results.

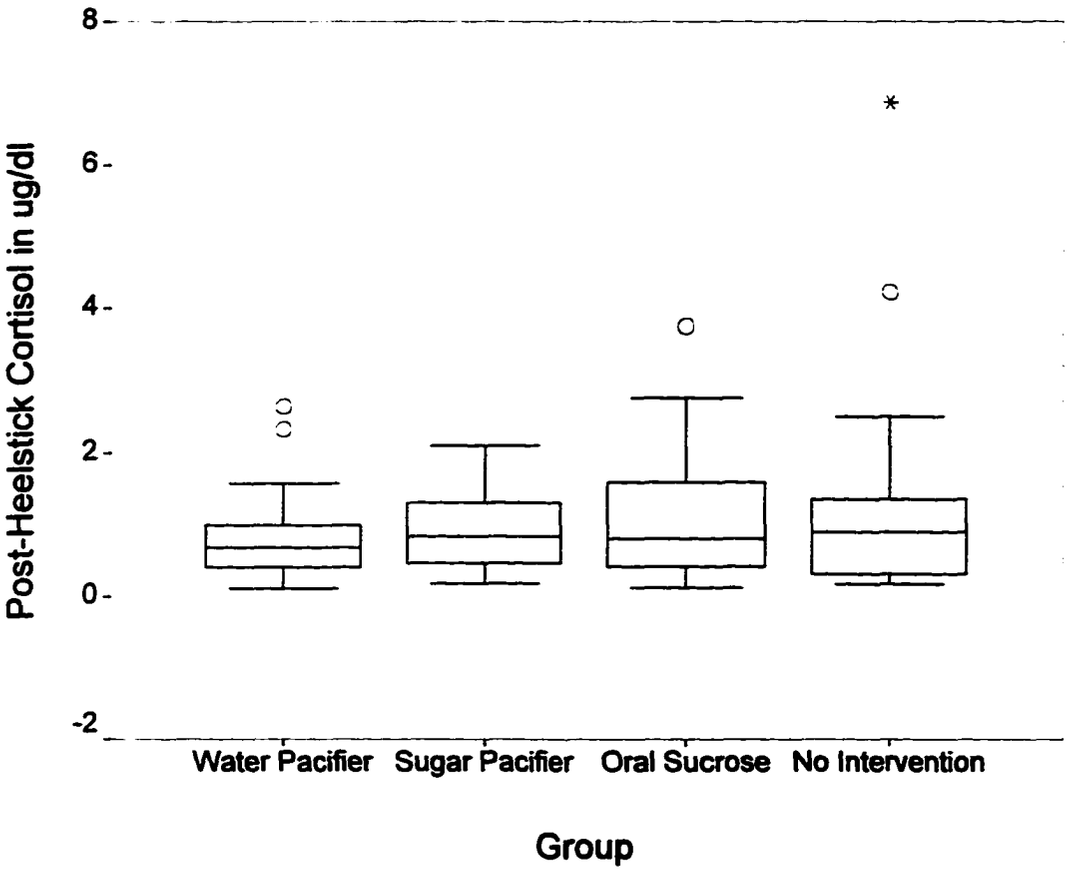

Figure 2. Post-heelstick cortisol by group (n = 21 per group). The box represents the interquartile range. The dark line in the box indicates the median. The whiskers show the range of values that fall within 1.5 hingespreads of the interquartile range. The open circles indicate outliers more than 1.5 box-lengths from the 75th percentile, the asterisk an extreme outlier more than 3 box-lengths from the 75th percentile.

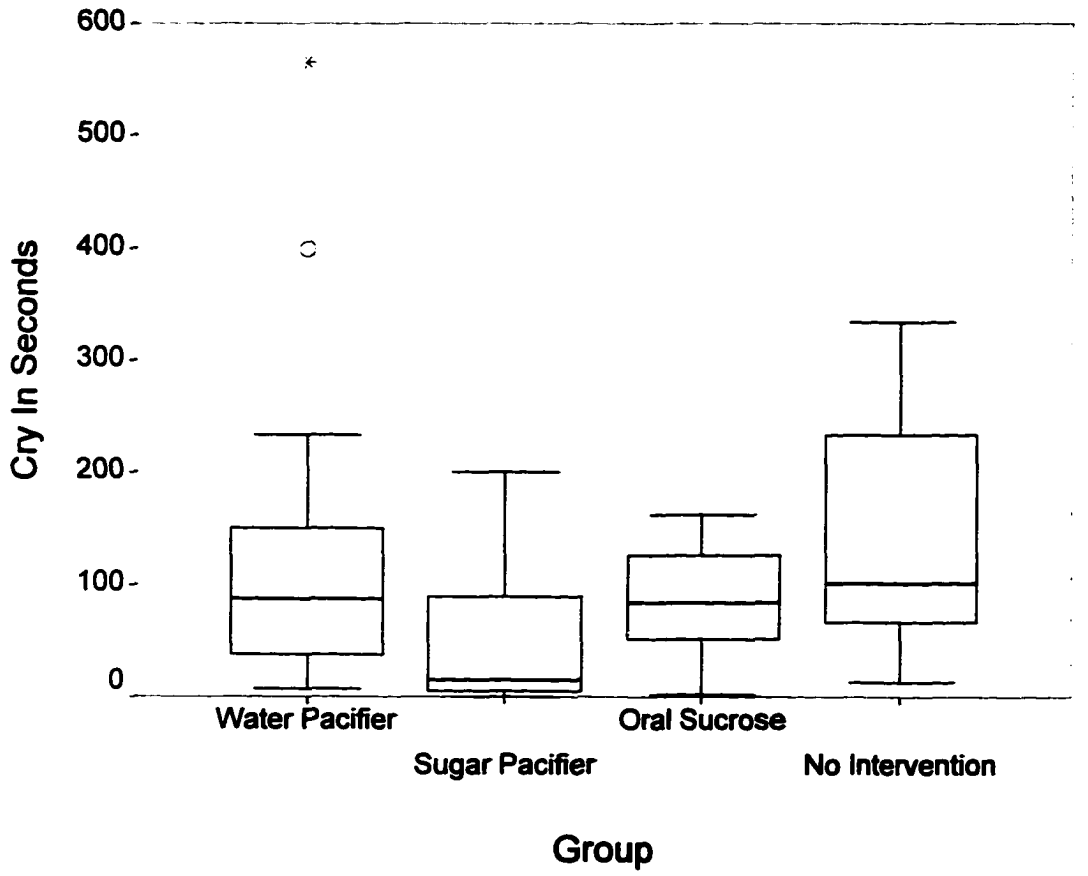

Figure 3. Duration of cry by group (n = 21 for each group). Cry was analyzed using a square root transformation to normalize the data. Data in this figure are not transformed. The box represents the interquartile range. The dark line in the box indicates the median. The whiskers show the range of values that fall within 1.5 hingespreads of the interquartile range. The open circle indicates an outlier value more than 1.5 box-lengths from the 75th percentile, the asterisk an extreme outlier more than 3 box-lengths from the 75th percentile.

Change scores. Results of MANOVA were not significant when change scores for vagal tone (from baseline to heelstick procedure) or cortisol (from pre- to post-heelstick) were analyzed. Examining the components of the vagal tone change scores, one-way ANOVAs on vagal tone change from baseline to intervention and change from intervention to heelstick procedure were not significant between groups.

Although ANOVA did not reveal significant group differences the scores revealed interesting trends (see Table 5). Vagal tone decrease from baseline to intervention was greatest in the oral sucrose solution group, followed closely by the sugar coated pacifier group. The water moistened pacifier group showed a smaller decrease from baseline. The no intervention group showed the smallest decrease in vagal tone from baseline values.

Decrease in vagal tone index from intervention to heelstick procedure was greatest in the no intervention group, less in the sugar coated pacifier group, followed closely by the water moistened pacifier group. The oral sucrose solution group showed only a minimal decrease in vagal tone from intervention to heelstick procedure.

Table 5

Changes in Vagal Tone: Baseline to Intervention, Intervention to Procedure

Change	Water Pacifier	Sugar Pacifier	Oral Sucrose	No Intervention	Total Sample
Baseline to intervention	-0.3105	-0.4802	-0.5136	-0.1200	-0.3561
Intervention to procedure	-0.3105	-0.3581	-0.0781	-0.4585	-0.3013

Note. No statistically significant differences were present between groups.

Sub-hypotheses

In order to evaluate the relative efficacy of each intervention, this study addressed several sub-hypotheses. Findings were presented above. The following presents a synopsis of these findings as pertinent to each sub-hypothesis.

H_1: infants offered a sucrose coated pacifier demonstrated decreased pain behaviors when undergoing painful procedures compared those who were offered no intervention.

The sugar coated pacifier group demonstrated a statistically significant shorter duration of cry and lower vagal tone index at heelstick than the no intervention group.

H_2: infants offered a sucrose solution orally demonstrated decreased pain behaviors when undergoing painful procedures compared to those who were offered no intervention.

No statistically significant differences were demonstrated between the oral sucrose solution group and no intervention group.

H_3: infants offered a water moistened pacifier demonstrated decreased pain behaviors when undergoing painful procedures compared to those undergoing painful procedures who were offered no intervention.

No statistically significant differences were demonstrated between the water moistened pacifier group and the no intervention group.

H_4 infants offered a sucrose coated pacifier demonstrated decreased pain behaviors compared to those who were offered a sucrose solution orally.

The sugar coated pacifier group demonstrated statistically significant lower vagal tone index during heelstick than the oral sucrose solution group.

H_5 infants offered a sucrose coated pacifier demonstrated decreased pain behaviors compared to those who were offered a water moistened pacifier.

The sugar coated pacifier group demonstrated a statistically significant shorter duration of cry than the water moistened pacifier group.

Associated Question: Effect of Treatment Group on Vagal Tone Response over Time

The effect of study treatments on the infant's recovery post heelstick procedure was not directly related to the study hypotheses. However, the vagal tone data were examined to evaluate the effect of treatment on vagal tone response over time and infant recovery from heelstick (see Table 6).

Examining vagal tone index over time (baseline, intervention, heelstick procedure, and four 5 minute epochs post heelstick procedure) with repeated measures ANOVA demonstrated statistically significant group differences (F (3, 80) 3.292, $p = .025$). Post hoc analysis with Bonferroni test of multiple comparisons revealed statistically significant group differences at intervention between the sugar coated pacifier group and no intervention group (mean difference = -.8695, $p = .019$), at heelstick procedure as discussed above, and post heelstick procedure between the sugar coated pacifier group and no intervention group at minutes 6 - 10 (mean difference = -1.0938, $p = .007$) and at minutes 11 - 15 (mean difference = -.9324, $p = .049$).

Vagal tone responses over time (baseline, intervention, heelstick procedure, post-procedure epochs) were significant to a quadratic order polynomial. Figure 4 visually

Table 6

Vagal Tone Index During Post Heelstick Epochs

VTI in ln/ms^2	Water Pacifier	Sugar Pacifier	Oral Sucrose	No Intervention	Total Sample
Minutes 6 - 10					
mean	3.0905	2.3986	3.1319	3.4924	3.0283
SD	.9053	.8426	1.573	1.1278	1.1012
Minutes 11 - 15					
mean	2.9457	2.5324	3.0605	3.4648	3.0008
SD	1.0163	.8603	1.1969	1.3280	1.1441
Minutes 16 - 20					
mean	3.0162	2.7210	3.1633	3.5957	3.1240
SD	1.1794	1.0688	1.0603	1.3854	1.2019
Minutes 21 - 25					
mean	3.1429	2.9343	3.4129	3.6062	3.2740
SD	1.1082	.8226	1.0886	1.3344	1.1135

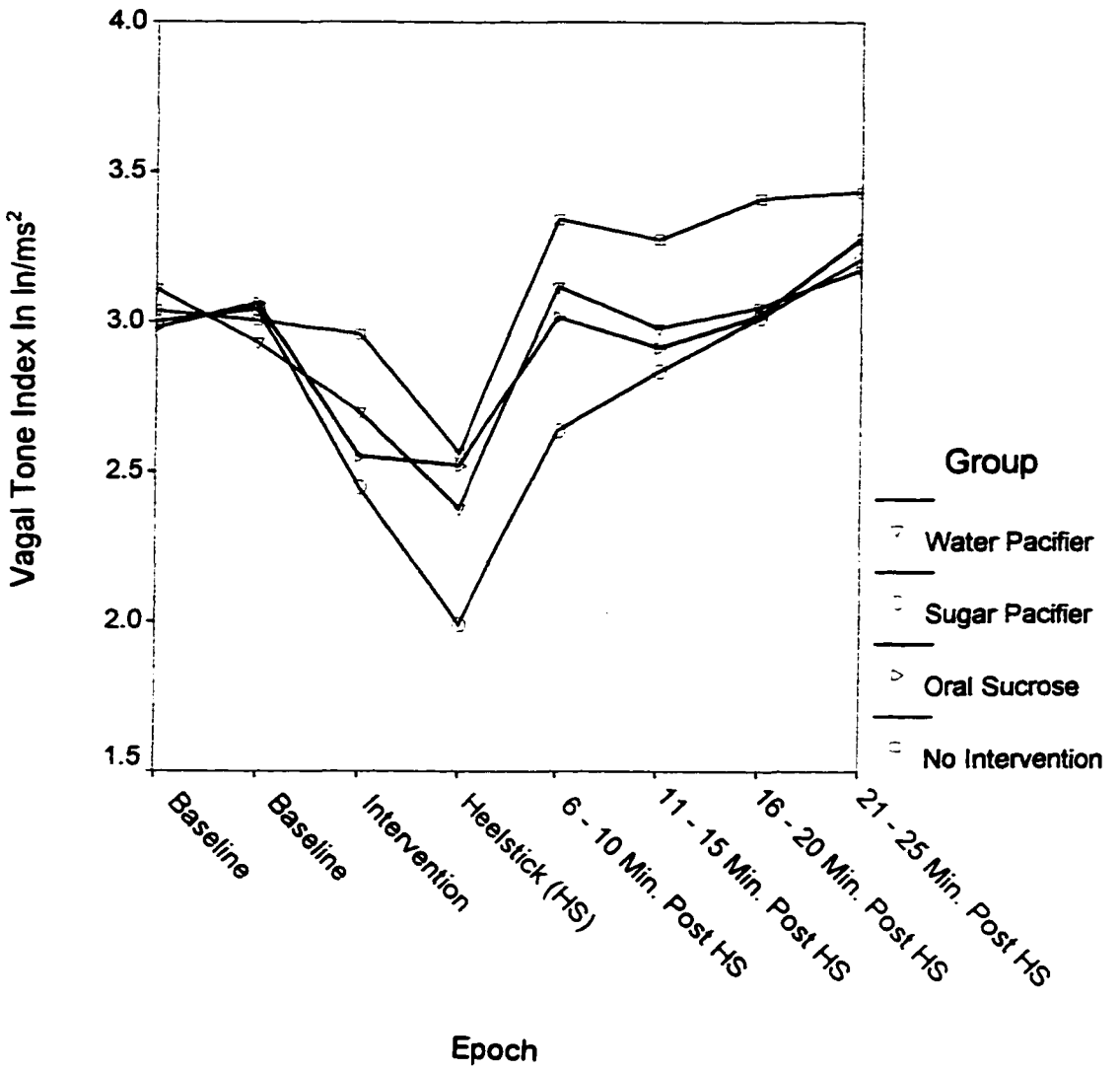

Figure 4. Vagal tone index (ln/ms²) over sequential epochs by group. Baseline vagal tone was used as a covariate. All epochs were 5 minutes long except the intervention epoch which had a duration of 3 minutes. The sugar coated pacifier and oral sucrose solution groups showed statistically significant trends.

demonstrates a decrease in vagal tone index in all groups. The water moistened pacifier and control groups have no statistically significant trend. The sugar coated pacifier group and oral sucrose group showed statistically significant trends from a flat line.

Influence of Demographic Characteristics on Study Measures

Previous literature suggests that demographic characteristics may influence pain response. To evaluate the influence of demographic characteristics on study results, Pearson Chi-Square test was completed on nominal data and ANCOVA on interval and ratio data.

Pearson Chi-Square test between groups was not significant at 0.05 for the demographic characteristics of gender, ethnicity, type of anesthesia received for labor and delivery, administration of narcotics to the mother prior to delivery, type of delivery, history of previous heelsticks, or history of circumcision.

ANCOVA demonstrated no significant differences when APGAR scores at 1 and 5 minutes, age at heelstick, gestational age, and number of times the heel was lanced during data collection were covaried with the dependent variables and treatment group.

Birth weight. When birth weight was covaried with cortisol change and treatment group, birth weight was a significant covariate (F (3, 79) = 9.246, p = .003), but there was no main effect of treatment group.

There was a significant negative correlation between magnitude of cortisol response and birth weight. This was demonstrated in analysis of both cortisol change and birth weight (r = -.295, p =.006) and post-heelstick cortisol level and birth weight (r =

-.265, p = .015). This indicates that lower birth weight is associated with higher levels of cortisol reactivity. Pre-heelstick cortisol level was not significantly correlated with birth weight (r = .025).

Procedure length. Results of ANCOVA indicated that the length of time it took to perform the heelstick and blood collection was a significant covariate with the square root transformation of cry (F (3, 79) = 5.587, p = .021). There was a significant positive correlation (r = .328, p = .002) of square root of cry and procedure length, the longer the procedure the more the infant cried. Adjusting for the length of procedure, the main effects of treatment group was still significant (F (3, 79) = 4.743, p = .004) for cry.

Discussion of Findings

This study provides information on the comparative efficacy of a water moistened pacifier, a sugar coated pacifier, 2 cc of a 12% oral sucrose solution, and no intervention as methods of pain relief during heelstick in newborns. Discussion of data analysis findings in relation to the study hypotheses will be addressed. The effect of treatment on recovery and the influence of other factors are also discussed.

Correlation of dependent variables. The square root transformation of cry and vagal tone index at heelstick procedure were correlated. Other observations of cry, cortisol, and vagal tone were not correlated.

Vagal tone responds quickly to pain and rapidly returns to near baseline after termination of the painful stimuli (Porter, et al., 1988). The majority of infants cried during the painful procedure when their heel was lanced, but stopped shortly after the heelstick procedure was over, if not before. Vagal tone was measured for another 20

minutes after the painful procedure was completed but only three infants were still crying for a short time into the first post-heelstick vagal tone epoch. Therefore, the correlation between cry and vagal tone at heelstick procedure, but not at other vagal tone epochs, was anticipated.

Lack of correlation between cortisol reactivity and the other two dependent variables may be due to the wide range of cortisol reactivity response demonstrated in the infants. Group differences in cortisol reactivity were not detected either. It is postulated that cortisol specimen collection technique with use of salivary stimulants or timing of sample collection may have influenced results. The pain stimulus may not have been strong enough to trigger the cortisol stress response, although other studies have detected cortisol reactivity in response to heelstick (Gunnar, et al., 1992). It may also be that the interventions in this study did not influence perception of the pain experience.

Interpretation of Findings in Relation to Study Hypotheses

Based on previous research, directional hypotheses were proposed to evaluate the effectiveness of selected interventions over no intervention. Sucking alone has been shown to decrease pain behaviors (Campos, 1989; Gunnar, et al., 1984; Miller & Anderson, 1993) possibly by "closing the gate", or blocking the pain impulses from traveling up to the higher perceiving centers in the brain. Because sucrose is thought to be mediated through the opioid pathways (Blass, et al., 1987; Blass & Hoffmeyer, 1991), thus being more potent than simple mechanical stimuli, it was hypothesized that the two sucrose groups would demonstrate fewer pain behaviors than the other two groups.

Augmenting sucrose with sucking would provide an additive effect making a sugar coated pacifier most effective in decreasing the presence of pain indices.

Because the three pain measures, duration of crying, vagal tone reactivity, and cortisol reactivity demonstrated different, or no, group differences, they will be discussed separately.

Cry. Sucrose administered via a sugar coated pacifier was effective in reducing duration of crying over the water moistened pacifier and control groups in this study. Although the oral sucrose solution group demonstrated a shorter duration of crying (85 seconds) than the water moistened pacifier (126 seconds) or control groups (133 seconds), this was not statistically significant. Post hoc analysis of homogeneous subsets with Tukey HSD revealed two subsets: 1) the sucrose solution group with the sugar coated pacifier group and 2) the sucrose solution group with the water moistened pacifier and control groups. This demonstrates the trend toward reduced crying in the oral sucrose solution group. Previous research has found that administration of an oral sucrose solution effectively decreases crying associated with painful procedures (Blass & Hoffmeyer, 1991; Bucher, et al., 1995) but decreased crying may be dependent on the concentration of the sucrose solution with 50% and 25% solutions significantly decreasing crying over 12.5% or no sucrose (Haouari, et al., 1995). The 12% sucrose solution used in this study may not have been concentrated enough to produce statistically significant group differences, although clinically it may have a degree of effectiveness.

Vagal tone. Infants in the sugar coated pacifier group demonstrated statistically significant lower vagal tone during the heelstick procedure than the oral sucrose and no

intervention groups. Post hoc analysis of homogeneous subsets with Tukey HSD revealed two subsets: 1) the sugar coated pacifier group with the water moistened pacifier group and 2) water moistened pacifier group with the sucrose solution and no intervention groups. This demonstrates a trend toward lower vagal tone in the water moistened pacifier group.

It was presumed that infants experiencing the most pain would demonstrate the greatest decrease in vagal tone, reflecting the fact that pain is a stressor. It may be that the sugar coated pacifier group, which had statistically significant lower vagal tone during heelstick, did experience the most pain. However, this did not appear to be the case, since infants in the sugar coated pacifier group demonstrated lower vagal tone values and the shortest duration of cry, both measures manifest to a statistically significant degree. Also, vagal tone dropped in the three intervention groups during intervention, prior to application of the noxious stimuli.

Decreased vagal tone is associated with stressors such as pain but also occurs with attention demanding tasks in which the infant must focus (Porges, et al., 1996). Sucrose being sweet has salience, it seizes attention through the gustatory system. Sucrose also causes calming through an endogenous opioid system and activates suckling-feeding mechanisms (Blass, et al., 1989). Sucking promotes behavioral organization (Medoff-Cooper & Ray, 1995; Pickler & Frankel, 1995) and helps an infant self-sooth (Kimble, 1992). Infants in the sugar coated pacifier group were provided the double impact of sensory stimulation through sucking and orogustatory stimulation from the sugar. This may have helped organize behavior and focus the infant's attention resulting in a greater

decrease in vagal tone from task attention rather than indicating higher pain levels. The fact that vagal tone was statistically significantly lower in the sugar coated pacifier group than the no intervention group during intervention, prior to the noxious stressor, further supports this theory. Infants in the two groups that had a single intervention (pacifier or oral sucrose) also demonstrated a decrease in vagal tone from baseline to intervention, although it was not as great as the pacifier plus sucrose group and not statistically significant.

Infants in all groups demonstrated a decrease in vagal tone index from baseline to heelstick procedure. The trends in vagal tone reduction, although not statistically significant, are noteworthy. The oral sucrose solution group demonstrated the greatest decrease in vagal tone from baseline to intervention, then a minimal decrease from intervention to heelstick procedure (see Table 5). The no intervention group demonstrated minimal vagal tone decrease from baseline to intervention, then the greatest degree of decrease from intervention to heelstick procedure. Thus, the two groups had similar vagal tone values to start and at heelstick procedure, but the stimulus for decrease was different (sucrose versus noxious stimuli).

Infants in the water moistened pacifier group showed a trend toward decreased vagal tone although this was not statistically significant. This may indicate that sucking impacts vagal tone more than 12% sucrose administered orally. The 12% sucrose concentration may not be potent enough to impact vagal tone, but changes might be detected with higher sucrose concentrations (Haouari, et al., 1995). Alternatively, since vagal tone demonstrated the greatest degree of decrease in the oral sucrose group from

baseline to intervention, then minimally from intervention to heelstick procedure, it may indicate that oral sucrose rapidly focused the infant's attention to the greatest degree and these infants experienced less pain during the painful procedure.

Based on the pattern of vagal tone response seen in the sample, decreasing in all infants during heelstick (with infants in the double intervention group demonstrating the lowest values, the single intervention groups demonstrating mid-range values, and no intervention infants demonstrating the highest values), it seems to indicate that vagal tone is indexing focused attention. Whatever the source, noxious or non-noxious stimuli, vagal tone decreases in response to attentional focus. Providing multiple non-noxious stimuli is more powerful than a single focus, thus dividing attention between multiple stimuli results in a greater decrease in vagal tone. If a greater attentional focus is provided than the noxious stimuli, attention can be focused away from the pain resulting in decreased perception of the painful event.

Cortisol. No differences in cortisol values were detected between groups in this study. It may be that there were no group differences as a result of treatment but, since the other study measures demonstrated group differences, other factors may be influencing the lack of group variation. These factors include individual differences in cortisol response, infant state prior to data collection, and saliva sample collection techniques.

The hypothalamic-pituitary-adrenocortical (HPA) axis plays a role in regulating the newborn's response to the environment. There is a wide range in the pattern, timing, and degree of individual differences in reactivity to stress and in HPA response (Gunnar, et al., 1989; Lewis, 1992). Some infants react intensely to a perturbation, while others react less

so to the same stimulus (Lewis, 1992). Saliva was collected 25 minutes post heelstick to detect cortisol secretion in response to the stressor at the time when the majority of infant's show elevations in their response (Gunnar, 1992). Saliva collection at 25 minutes post stressor may have caught some infants on the upswing of the cortisol response, some at the peak, and some on the decline, thus diluting the ability to detect group differences.

Cortisol levels obtained before stimulation are influenced by the behavioral state of a newborn in the 30 minutes prior to sampling (Gunnar, 1992). Although this study attempted to control for infant state by bringing all infants to a quiet alert state at the beginning of data collection, the infant's level of arousal preceding data collection may have influenced pre-heelstick cortisol values. After the heelstick, infants were loosely covered with a blanket and not disturbed. The majority fell asleep, some stayed awake. Differences in level of arousal may have influenced post heelstick procedure cortisol values, in addition to the degree of cortisol response to the stressor of heelstick.

Sample collection techniques may have reduced the ability to detect group differences in cortisol values. The use of oral stimulants to promote salivation may attenuate cortisol level changes in response to mild to moderate challenge (Schwartz & Granger, 1997). This can decrease the ability to detect cortisol-behavior associations. Powdered drink mixes (e.g. Kool-Aid®, Crystal Light® crystals) contain citric acid that stimulates salivation and are commonly used in studies that require saliva collection from children. Inconsistent use and dosage of the stimulant to generate an adequate saliva sample impacts assay findings (Schwartz & Granger, 1997).

Newborns produce very little saliva (Gunnar, 1992). The present study used 10% citric acid solution to stimulate salivation in newborns. The citric acid solution was chosen because it did not contain the artificial ingredients of powdered drink mixes and in an attempt to standardize the dose of oral stimulant given to the infant. The effect of oral stimulants on assay results was recognized midway through data collection (personal communication, D. A. Granger, 8/96). At this point it was decided, in conjunction with the director of the laboratory performing the assays, to continue using the original study protocol trying to use only 1 drop of citric acid solution, instead of 1 - 2 drops. The use of citric acid to generate saliva flow in this study may have attenuated the magnitude of treatment group differences. This, in conjunction with individual variation in cortisol response, may be the reasons that group differences were not detected.

Interpretation of Treatment Effects on Post Heelstick Recovery

As discussed previously, analysis of vagal tone during the heelstick procedure (minutes 0 - 5) demonstrated significantly lower vagal tone in the sugar coated pacifier group than the control and oral sucrose solution groups. Repeated measures ANOVA using vagal tone index revealed statistically significant group differences with the sugar coated pacifier group demonstrating lower vagal tone than the no intervention group post heelstick procedure at minutes 6 - 10 and at minutes 11 - 15. For these two vagal tone epochs, post hoc analysis of homogeneous subsets with Tukey HSD revealed two subsets: 1) the sugar coated pacifier group with the water moistened pacifier group and the oral sucrose solution group and 2) the water moistened pacifier group with the sucrose solution and control groups. This demonstrates the differences between the sugar coated

pacifier group and control, but no statistically significant difference between the water moistened pacifier group or the oral sucrose solution group with the other groups. Viewing the response over time, the two groups who had a single intervention (pacifier or oral sucrose) demonstrated somewhat similar vagal tones in the mid-range between the no intervention group with higher vagal tone, and the sucrose coated pacifier with lower vagal tone. For the single intervention groups, this may be explained by the fact that only one modality was stimulated, thus seizing and focusing attention but not to the extent of both together. It may also be that these interventions did not impact the pain experience.

Decreased vagal tone is associated with stressors such as pain but also occurs with attention demanding tasks in which the infant must focus (Porges, et al., 1996). Infants in the sugar coated pacifier group were provided the double impact of sensory stimulation through sucking and orogustatory stimulation from the sugar. This may have helped organize and focus the infant's attention resulting in a greater decrease in vagal tone attributable to task attention rather than indicating higher pain levels. Sucking and sucrose both appear to cause the infant to focus attention revealed by lower mean vagal tone values than the nonintervention group. In this case, lower vagal tone may indicate greater behavioral organization and lower pain levels. The ability to detect group differences at 15 minutes post heelstick procedure indicates that the sugar coated pacifier has a relatively long duration of efficacy.

Vagal tone in all groups except the sugar coated pacifier group rebounded to baseline or greater values within 5 minutes post-heelstick procedure. The sugar coated pacifier group did not regain baseline values until 16 minutes after the painful procedure.

Since vagal tone response to painful stimuli is rapid with a rapid return to baseline, this may indicate sustained attention with slow offset of the effects of the sugar coated pacifier. Infants in the no intervention group showed the greatest rise above baseline levels and during minutes 11-25 post heelstick the no intervention group was visually distinct and higher than the three intervention groups.

Other Factors Influencing Outcome Measures

Birth weight and length of heelstick procedure significantly covaried with outcome measures used to evaluate pain response in the infant. Neither had an impact on the main effect of treatment group.

Birth weight. Birth weight is considered in calculating risk level in newborns, with lower birth weight being associated with increasing risk of adverse outcomes. Low birth weight is defined as birth weight <2,500 grams (Doussard-Roosevelt, et al., 1997). Although infants in this study were relatively healthy newborns with a birth weight of at least 2,500 grams, birth weight impacted magnitude of cortisol response. Lower birth weight infants showed a greater degree of cortisol reactivity after heelstick. As discussed previously, wide variation exists in the pattern of individual reactivity to stress but, based on the correlation between lower birth weight and cortisol, birth weight affected cortisol response more so in lower birth weight infants in this study. In an effort to stabilize HPA response in transitioning to extrauterine life, birth weight appears to play a role that needs further research.

Procedure length. The longer the heelstick procedure took, the longer the infants in this study cried. Empirically this is predictable, the longer the infant is exposed to

noxious stimuli, the more aroused they become. Length of heelstick procedure had no impact on treatment group differences.

Summary

MANOVA and post hoc analyses revealed that:

- infants in the sugar coated pacifier group had a statistically significantly shorter duration of cry than those in the water moistened pacifier group or control group;
- infants in the sugar coated pacifier group had statistically significantly lower vagal tone index during intervention, prior to heelstick, than those in the control group;
- infants in the sugar coated pacifier group had statistically significantly lower vagal tone during the heelstick procedure than those who received 2 cc of 12% oral sucrose solution or the control group;
- infants in the sugar coated pacifier group had statistically significantly lower vagal tone for 15 minutes post heelstick procedure than the control group.

ANCOVA demonstrated significant covariation of birth weight with cortisol, and heelstick procedure length with cry. Adjusting for the effects of these covariates did not impact MANOVA findings: infants in the sugar coated pacifier group cried less than those in the water moistened pacifier and no intervention groups and had lower vagal tone during heelstick than those who received oral sucrose solution or no intervention.

These findings may be due to a greater degree of organized behavior and lower degree of pain perceived by the infants as a result of the intervention. The interventions may divide the infant's attention, offering a competing force to the pain stimuli. If the infant's attention can be shifted to sufficient degree, the perception of pain can be

decreased. This may indicate a high degree of cognitive functioning in a newborn, more than they are generally thought to possess.

Offering a sugar coated pacifier for mildly painful procedures appears to be effective in reducing the level of pain perceived by the infant over no intervention. Although not statistically significant, infants in the water moistened pacifier and 12% oral sucrose solution groups cried for shorter periods of time and had lower vagal tone values than infants offered no intervention. Offering a water moistened pacifier or administration of 2 cc of 12% sucrose appears to be more effective in reducing pain than no intervention, although not as effective as a sugar coated pacifier.

CHAPTER V: Summary, Conclusions, Recommendations

Pain is a clinical problem which is difficult to evaluate and, therefore, to manage in pre-verbal infants. This chapter will summarize the problem researched in this dissertation including pertinent literature, the study and findings of data analysis. Implications for practice and recommendations for future research will also be discussed.

The Problem

It is only within the past two decades that the medical community has acknowledged that infants have the neuroanatomical ability to experience pain. In fact, research has demonstrated that, when subjected to the same stimulus, infants experience pain to an even greater degree than adults (Fitzgerald, 1991a). Yet pain in infants is often poorly managed, often with deleterious consequences such as physiologic instability, poor oxygen saturation, alterations in cerebral blood flow potentially causing hemorrhage, and long term alterations in processing of pain stimuli . There is a serious need for identification of effective, empirically based pain management techniques for infants.

Initial studies suggested that sucrose is mediated through the opioid pathway (Blass, et al., 1987; Blass, et al., 1989; Blass & Hoffmeyer, 1991). Since then there has been great interest in using sucrose as an analgesic in infants. Sucrose is readily available, easy to use, has few if any side effects, may be more effective than traditional

nonpharmacologic pain interventions, and can be implemented as an independent practice decision by nurses.

Study aims. This experimental study examined the efficacy of a water moistened pacifier, a sugar coated pacifier, 2 cc of a 12% oral sucrose solution, and no intervention for pain management during heelstick in neonates 12 to 32 hours of age. All four are used in clinical practice. This study was designed to evaluate the effects of sucking alone and sucrose alone, to evaluate the effect of the two to augment each other, and to evaluate the relative efficacy of each of the three interventions over no intervention in alleviating mild procedural pain.

Synopsis of the Literature

Health care practitioners have taken the initial studies using oral sucrose solution and altered the technique by using sucrose in the form of granulated sugar instead of the sucrose solution. The sugar is administered by coating a pacifier with sugar and offering this to the infant. The vehicle by which the granulated sugar is delivered, a pacifier, adds a sucking component to the technique.

Sucrose and sucking work in the central nervous system through different methods. Sucrose works via the opioid receptor pathway. It is thought to stimulate release of endogenous opioids (Blass, et al., 1987) which then occupy opioid receptor sites, thus inhibiting transmission of pain impulses. Sucking, as explained by the Gate Control Theory of pain, works by stimulating the Aα fibers of the nerves which are sensitive to light mechanical stimulation. The signal travels to the substantia gelatinosa in the dorsal horn of the spinal cord before the slower moving pain signals transmitted

through Aδ and C fibers. Transmission of Aα fiber impulses activates the gate to close, thus preventing peripheral transmission of pain signals from Aδ and C fibers to the dorsal horn and from there to higher pain perceiving centers in the brain (Melzack & Wall, 1965).

Both sucking (Campos, 1989; Miller & Anderson, 1993) and sucrose in solution (Blass & Hoffmeyer, 1991; Bucher, et al., 1995) have been studied separately and appear to be effective in managing mild, procedure related pain. Used together, sucking and sucrose may augment each other providing even more effective pain relief for the infant.

Study Measures Used to Evaluate Pain

The three measures used to assess the pain experience in this study: duration of crying, vagal tone, and cortisol, evaluate different components of the individual pain response in order to capture various aspects of the experience in the non-verbal population being studied.

Crying. Crying in an infant indicates some degree of distress-arousal (Fuller, 1991). Many clinicians and researchers use crying as a measure of pain (Allen, et al., 1996; Fuller, et al., 1996; Johnston, et al., 1993). Crying has face validity as a pain measure and is one of the most widely accepted indicators of pain in infants (Porter, 1993); therefore, it was chosen as a behavioral indicator of pain in this study.

Vagal tone. Vagal tone is a heart rate pattern that detects the parasympathetic response to nociceptive stimuli. Generally, the parasympathetic system is inhibited during the acute response to nociceptive stimuli. Shifts in heart rate that occur in response to stressors reflect the rhythmic "gating" of vagal effects on heart rate by respiration, and the

magnitude of change is associated with vagal efferent tone to the heart. Therefore, the greater the amplitude of heart rate variation with respiration (the respiratory sinus arrhythmia or RSA), the greater the vagal tone. One measure of RSA, vagal tone index, employs a complex statistical technique for quantification of the amplitude of RSA using a unique time series method (Porges, 1985). Measurement of vagal tone as an index of pain, as opposed to measuring heart rate or heart period, eliminates the influence of non-neural factors and provides data that are more specific to the pain itself because vagal tone is directly influenced by central nervous system control (Porter 1989). Vagal tone appears to be sensitive to differences in stimulus intensity and to discriminate between nociceptive and non-nociceptive stress responses (Porter, et al., 1988).

Cortisol. The body reacts to the stress of pain by secreting increased amounts of catecholamines, growth hormones, glucagon, cortisol, and other corticosteroids (Anand, et al., 1990). Painful stimuli triggers elevations in cortisol levels (Lewis & Thomas, 1990), but administration of analgesia to block pain signal transmission produces significant decreases in cortisol reactivity (Stang, et al., 1988). Healthy newborns are able to differentially respond to qualitatively different stressors such as pain versus non-painful perturbation (Gunnar, et al., 1992). Cortisol is useful to measure the adrenocortical response to the stress of painful procedures because it can be obtained non-invasively using saliva. Use of salivary cortisol avoids exposing infants to unnecessary invasive procedures such as heelstick or venipuncture, which is preferable for research.

Pain Management

Effective management of pain is essential to prevent the deleterious consequences associated with untreated pain. Infants are at particular risk because of their inability to physically escape from inflicted pain and because of limitations in their ability to communicate the severity of their pain.

Opioids and other analgesics can be used for pharmacologic management of pain in infants, but practitioners are often reluctant to use them because of associated side effects such as respiratory depression or altered drug metabolism. Thus, the infant often experiences severe or ongoing pain before pharmacologic interventions are used.

Nonpharmacologic pain interventions such as distraction, positioning, swaddling (Campos, 1989), relaxation, and music therapy may be effective for managing mild pain. These may also be effective adjuncts, to augment pharmacological interventions, for management of moderate to severe pain (Greenberg, in press). Sucking is another nonpharmacologic intervention that attenuates signs of behavioral distress in neonates during invasive procedures (Campos, 1989; Field & Goldson, 1984) and contributes to physiological adaptation (Miller & Anderson, 1993). Nonnutritive sucking also helps an infant organize behaviors, adapt to stimuli (Kimble, 1992; Pickler & Frankel, 1995) and may increase the release of pain-alleviating neurotransmitters, thus aiding in stress reduction (Field, 1993). Therefore, nonnutritive sucking may augment other interventions aimed at pain alleviation and may provide the benefit of stress reduction.

Sucrose is thought to be mediated through the opioid pathways (Blass, et al., 1989; Blass, et al., 1987), therefore, possessing some pain alleviating properties and

offering a more potent non-pharmacologic intervention for pain than typically used. The analgesic efficacy of sucrose may be a function of solution strength. Sucrose concentrations of 7.5% appear to have a pain alleviating effect similar to water, which is better than controls but not statistically significant (Rushforth & Levene, 1993). Concentrations of 12% may reduce pain manifestations, but as sucrose concentration increases to 25% and 50% pain manifestations decrease (Haouari, et al., 1995). A 12.5% concentration of sucrose solution was not statistically significant from the sterile water group, but overall there was a trend to reduction in crying times with increasing concentration of sucrose solution (Haouari, et al., 1995). The analgesic efficacy of sucrose may also be related to the presence of nonnutritive sucking.

Given the risk of opioid administration in neonates, sucrose may provide a lower risk alternative with similar efficacy. Sucrose is readily available and inexpensive. Offering a sucrose coated pacifier has advantages in that it can be done quickly and easily, and the nurse can implement it as an independent practice decision.

Methodology

A randomized, complete block experimental design was used to evaluate the efficacy of sucrose, administered via a coated pacifier, in reducing pain behaviors compared to sucrose solution delivered via syringe, a water moistened pacifier, and no intervention. The dependent variables were three measures used to assess the pain experience in infants: duration of cry, vagal tone reactivity, and salivary cortisol reactivity.

Eighty-four infants undergoing the painful procedure of heelstick as part of a routine blood sample collection, who met selection criteria, and whose parents gave

informed consent were studied. Selection criteria were formulated to obtain a homogeneous sample of healthy term newborns.

In an attempt to standardize the painful stimulus, all heelsticks were performed by one phlebotomist. See Appendix D for a description of the Experimental Protocol.

Findings

MANOVA was used to examine differences between the 4 treatment groups for the 3 dependant variables. As a separate sub-question, vagal tone response post-heelstick procedure was examined in order to determine the effect of treatment on recovery time.

Statistically significant findings were demonstrated by infants in the sugar coated pacifier group compared to other groups. Infants who received a sugar coated pacifier had lower vagal tone during intervention, prior to heelstick, than those who received no intervention; lower vagal tone during the heelstick procedure than those who received 2 cc of 12% oral sucrose solution or no intervention; a shorter duration of cry than those who received a water moistened pacifier or no intervention; and lower vagal tone for 15 minutes post heelstick procedure than those who received no intervention.

Vagal tone decreases in response to both pain and attention demanding tasks. In this study, infants offered interventions that have been shown to reduce pain responses demonstrated lower vagal tone than infants offered no intervention. This finding, in conjunction with the fact that infants who demonstrated the lowest vagal tone had the shortest duration of cry and those with the highest vagal tone cried the longest, indicated that lower vagal tone in this study was a response to greater task attention and less pain perception.

Birth weight covaried significantly with cortisol and heelstick procedure length with cry. Neither covariate affected the main effects of treatment.

Examining the graphs of vagal tone responses over time, although not all statistically significant differences, revealed interesting findings (see Figure 4). Vagal tone responses on the graph were covaried with baseline vagal tone, thus all groups were very similar at the first two epochs, which were baseline measures. Visually observing vagal tone responses after baseline displayed distinct lines. Infants who received no intervention demonstrated higher vagal tone consistently over time, with the greatest decrease of any group during painful procedure and the greatest rise from heelstick procedure to the first post-procedure epoch. The two single intervention groups, pacifier alone and sucrose alone, had mid-range responses between the other two groups. Infants who received a sugar coated pacifier had the lowest vagal tone of any group. At 11 to 15 minutes post-heelstick procedure, values of the sugar coated pacifier group rose to approximate the values of the single intervention groups, the three intervention groups remained very similar through the 25 minutes of post-heelstick procedure data collection.

Conclusions / Implications for Practice

Findings from this study indicate that offering a sugar coated pacifier is more effective for management of mild pain in neonates than sucrose alone, a pacifier alone, or no intervention. Infants offered a sugar coated pacifier demonstrated significantly fewer pain responses, such as a shorter duration of cry and lower vagal tone, than infants offered no intervention. Single interventions showed trends toward decreased pain responses compared to those offered no intervention, although not statistically significant. Sucking

and sucrose presumably work through different pathways as demonstrated by the different patterns of response in cry and vagal tone. Infants offered a sugar coated pacifier cried significantly less than those offered a water moistened pacifier and had significantly lower vagal tone than infants given 2 cc of 12% oral sucrose solution.

Practitioners should offer a sugar coated pacifier to infants undergoing painful procedures. It is very simple to do, inexpensive, and may prevent the deleterious consequences of poorly managed pain. If parents are present, they can perform this and be empowered to help their child, instead of feeling helpless to prevent their child from suffering. Offering a sugar coated pacifier should be done in conjunction with, not in place of, other analgesics such as local anesthetics or opioids when these are routinely used or indicated.

Strengths and Limitations of the Study

Strengths. This study used both physiologic and behavioral measures to obtain a multi-dimensional assessment of the pain experience. This may provide a more accurate assessment of the pain experience in the non-verbal population studied than use of a single pain measure.

Data collection was standardized as much as possible. One researcher collected all data to minimize variation in data collection technique. One phlebotomist performed all heel punctures to standardize the pain stimulus. While his technique may have varied during the 8 months of data collection, the inter-individual variation should be less than if punctures were performed by many phlebotomists of varying skill levels.

Another strength of this study is that it included a fairly large sample of 84 infants. Initial power analysis, using the effect size for cry, determined that 20 infants would need to be included to detect group differences. Because the effect size for vagal tone and cortisol was not known, but it was postulated that it was not the extremely large one determined for cry, the power analysis was recalculated using a smaller effect size. Based on this, the sample size was increased to 84 infants.

This study was set up using a complete block randomized design. This was done to control for procedural variation that might occur due to familiarity with study protocol that might cause group differences if treatments were evaluated sequentially.

Limitations. Interpretation of the findings of this study is limited by a number of factors. First, although there is theoretical evidence to substantiate employment of the measures used to assess for the presence of pain in infants, these may not be valid and reliable indicators of pain in infants and as such may impact the accuracy of the results.

Secondly, even though an attempt was made to standardize the pain stimulus by having one phlebotomist perform all heelsticks, his technique may have varied slightly between infants, thus potentially subjecting the infants to different nociceptive stimuli.

A third limitation of the study is the inter-individual variability in the vagal tone and cortisol data. The power analysis done to determine sample size needed to achieve adequate power to detect group differences was based on the effect size for cry. Vagal tone and cortisol may be less sensitive to group differences because they depend on many factors in the individual infant. A larger sample size would have compensated for the

small effect sizes that may be associated with vagal tone and cortisol and provided additional power to determine statistically significant differences for these measures.

Another limitation was the difficulty in obtaining saliva from the infants for cortisol assay. A minimum of 0.5 ml of saliva was needed by the laboratory to conduct the assay. In the majority of infants, 0.5 ml of saliva was the maximum that could be obtained, even using 10% citric acid to stimulate flow. The use of citric acid may have also attenuated the ability to detect group differences (Schwartz & Granger, 1997).

The effect of prior exposure to painful procedures such as heelstick or circumcision could not be evaluated because of the small number of infants subjected to these procedures prior to data collection.

Lastly, given the inclusion criteria needed to obtain a homogeneous sample, generalizability of results is also limited. All data were collected in one institution. Findings are not generalizable to those populations who may be in even greater need of pain intervention such as premature infants, infants who were prenatally exposed to drugs, those who have congenital defects or are neurologically impaired.

Unique Contributions of this Study

This study builds on previous studies and provides new findings regarding pain intervention in infants. This study used vagal tone, a more precise measure of the infant's pain response than heart rate or heart period which have been most frequently used in previous studies. Therefore, results should be more accurate regarding the infant's pain response. This study also contributes new information regarding the interpretation of vagal tone response to stimuli in newborns.

The majority of previous studies administered sucrose solution via syringe. One study (Blass & Hoffmeyer, 1991) used a pacifier stuffed with gauze saturated with 24% sucrose solution during circumcision. Significantly less time was spent crying in the pacifier plus sucrose group than in the water moistened pacifier or no intervention groups (Blass & Hoffmeyer, 1991). This study further explored the use of a pacifier plus sucrose during heelstick and additionally compares the efficacy of this to both components separately: pacifier alone and sucrose alone. It was important to evaluate the efficacy of both sucrose and sucking alone since they may have an additive effect and provide more effective pain relief than either intervention alone.

This is the first study that evaluated the efficacy of simple table sugar in granulated form. Previous studies evaluated the efficacy of sucrose solution, which generally has to be prepared by the pharmacist. Evaluating the efficacy of granulated sugar is an important contribution because granulated sugar is more readily available to the clinician, thus increasing the chance that it will be implemented for pain management.

This study also adds unique information to the body of research by evaluating the impact of sucking and sucrose on recovery from painful procedure.

Previous studies have examined vagal tone as a response to noxious stimuli (Porter, et al., 1988) and stress (Fracasso, Porges, Lamb, & Rosenberg, 1994; Porges, 1992) and as an outcome predictor (Porges, et al., 1996). This study adds information regarding the aggregate response to simultaneous application of noxious and non-noxious stimuli. It also reveals exciting implications regarding the ability of newborns to

demonstrate more sophisticated cognitive functioning than generally presumed, indicated by increasingly lower vagal tone with more stimuli to divide attentional focus.

Recommendations for Future Research

Pain in infants is a topic that begs further research. The precise physiology of the nociceptive system and impulse transmission needs more elucidation. Assessment methods need to be developed and the reliability and validity of such determined. More research needs to be completed to examine various pain interventions and also their ability to potentiate each other. For example, opioids are appropriate for pain management after major surgery, but offering a sugar coated pacifier in conjunction with opioids may provide effective pain management with a decreased opioid dosage.

This study raises several issues. Biochemical analysis should be used to determine the actual concentration of sucrose administered by coating the pacifier with sugar. Is pain relief a factor of sucrose dose? Similar studies should be performed evaluating the efficacy of higher sucrose concentrations. What does the pattern of vagal tone response indicate? Porges and Lipsitt (1993) demonstrated that vagal tone decreased in response to sucking and ingestion of increasingly sweet concentrations of sucrose, no noxious stimuli were applied. In the study presented here, vagal tone decreased after ingestion of oral sucrose alone but then showed a minimal change in response to noxious stimuli. Offering a water moistened or sucrose coated pacifier triggered a decrease in vagal tone that further decreased in the next five minutes. Was this decrease part of the pattern in response to sucking and indicated a decreased amount of pain perceived? Or was it a response to the application of noxious stimuli? Was it a cumulative response to noxious

and non-noxious stimuli indicating increased attentional focus and decreased amount of perceived pain? To understand the implications of the vagal tone response pattern observed in this study, replication research is warranted using measures, more pain specific but very technically demanding, such as facial expression of pain or spectral analysis of cry.

The type of pain stimuli used in this study was one that neonates would experience in ambulatory settings and the results should be transferrable specifically for the procedure of heelstick in neonates. Sucrose may have different efficacy in older infants and children. Further research needs to be completed to determine the effectiveness of sucrose for pain relief in older infants and children as well as during immunizations, injection of local anesthetic prior to circumcision, intravenous catheter insertion, lumbar puncture, and other painful events, and post-operatively.

Does offering a sugar coated pacifier have any effect in a child who is receiving opioids or other analgesics such as non-steroidal antiinflammatory agents? Research is also indicated to evaluate the effectiveness of a sugar coated pacifier in reducing deleterious consequences of noxious, but non-painful, stimuli such as chest physiotherapy or positioning.

Other questions remain. Do premature infants respond in a similar manner to the use of sucrose? Does sucrose have any deleterious side effects on the immature metabolic system of the premature infant? How do infants of substance abusing mothers react, since they may have altered opioid metabolism? Does temperament or individual differences in pain response affect efficacy of interventions? How do older infants and children respond

to the use of sucrose? Increasing cognitive abilities impact reaction to pain. Does visual and/or auditory stimulation impact the effectiveness of pain relief and can these modalities be used in addition to, or instead of, sucking in the older child?

Summary

The procedure of heelstick may be sufficiently mild as a noxious stimulus to enable the infant to gate the pain stimuli and attend to other stimuli, such as sucking, whereas more potent painful stimuli would be insufficiently gated. Sucrose may function through the opioid pathways but not provide as effective pain alleviation as opioids, again making this appropriate for mildly painful stimuli but not stimuli causing more severe pain. Therefore, a sucrose coated pacifier may be optimal for mildly noxious procedures such as heelstick or injection of local anesthetic prior to more invasive procedures such as circumcision, but more invasive procedures demand more aggressive pain management.

This research demonstrates that offering a sucrose coated pacifier to an infant during a mildly painful procedure is effective in reducing pain responses. It is simple to implement and has a rapid onset of action. Appropriate pain management in infants is necessary to prevent deleterious physiologic consequences such as cerebral bleeds and negative changes in long-term pain processing. It also improves the quality of care delivered and reduces cost, both emotionally and fiscally. Clinical practice must be based on research, such as investigated in this study, in order to provide optimal care and comfort for infants, a population crying for relief.

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Appendix A

Copyright Permission for Figure 1

July 23, 1997

Julie Lawley
Permissions Department
W.B. Saunders Co.
The Curtis Center
Independence Square West
Philadelphia, PA 19106-3399

Dear Ms. Lawley,

I am requesting permission to include a figure from a text published by W.B. Saunders in my dissertation. The figure is from **Care of Children and Families: The Continuum of Care** by V. Bowden, S. Dickey, and C.S. Greenberg, **Figure 13-1: Transmission of the pain impulse in an infant.**

Thank you for your consideration.

Sincerely,

Cindy Smith Greenberg
24642 Via Tonada
Lake Forest, CA 92630

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W. B. Saunders Company Date 8/17/97

Appendix B

Data Collection Sheet

Subject # _____ date / time at start of data collection: _____

MOTHER

_____ history of narcotic or illicit drug use during pregnancy (EXCLUDE if yes)

_____ chronic or infectious disease processes during pregnancy (EXCLUDE if yes)

type of anesthesia prior to delivery

_____ none _____ local

_____ epidural _____ spinal

delivery

_____ vaginal _____ unplanned C/S

_____ planned C/S reason for C/S:_____

BABY

birth date & time _____ citric acid pre_____ drops

age at start of data collection _____hours citric acid post_____ drops

birth wt. _____ (EXCLUDE if ↓2500 or ↑4000 gms)

APGARs _____ (1 min) _____ (5 min) (EXCLUDE if ↓7)

est. gestational age _____ (EXCLUDE if ↓37 weeks)

congenital anomalies (EXCLUDE)

sex _____

ethnicity _____

number of previous heelsticks _____

circumcision_____ if yes, date and time_____

time of last feed in min. _____

number of times heel lanced during data collection _____

length of procedure _____ (from time heel is picked up until pressure released)

Appendix C

Experimental Protocol

Data collection was conducted in a separate room in the nursery. Only the infant under observation, the lab technician, and the investigator were present. If parents wished to accompany their infant they were allowed to do so. Parents were asked to refrain from speaking or touching their infant during data collection.

All infants were placed in a standard nursery bassinet with clear plexiglass sides which had the head propped up at a 30 degree angle. Infants were dressed in an undershirt and diaper was changed immediately prior to initiation of the protocol, and loosely covered with a blanket. If not already in an awake state, infants were awakened or calmed by the investigator or parent at the investigator's instruction. An awake state was defined as one where the infant had open eyes, was responding to the environment with quiet or active movement, and not crying.

Pre-heelstick salivary cortisol measurements were obtained just prior to baseline vagal tone data collection. The infant was placed on their right side. A dental pledget (Richmond; Charlotte, NC), 1.5 inches in length, was placed in the right side of the infant's mouth. Approximately half of the pledget was left hanging out of the infant's mouth and held on to by the investigator to minimize risk of aspiration. The infant was allowed to suck on the pledget for one minute to collect an adequate saliva sample. If an adequate sample was not obtained, 1 - 2 drops of a 10% citric acid solution was placed on the infant's tongue to stimulate salivation. The pledget was removed from the infant's mouth when wet and placed in a 6 cc syringe. The syringe plunger was compressed to extract approximately 1 - 1.5 milliliter (ml) of the saliva, minimum .5 ml, from the pledget. The saliva was placed in a 2 ml Bio-Freeze tube with inner screw threads (Costar Corporation; Cambridge, MA), labelled with subject's number and A to designate pre-heelstick sample. The sample was then frozen and stored at -20° C until sent for analysis.

After collection of the pre-heelstick saliva sample, three disposable Kittycat™ silver/silver chloride ECG electrodes (Sentry Medical Products, Irvine, CA) were placed on the infant. Electrodes were positioned one each on the front, upper, outer quadrants of

the right and left chest, near the shoulders and the ground lead on the left outer aspect of the lower abdominal quadrant. A disposable diaper wetted with warm water was positioned around the infant's left foot to stimulate vasodilation prior to blood specimen collection.

The Hewlett-Packard 78532 electrocardiograph recorder was turned on and clarity of the ECG signal transmission verified. If the ECG tracing was of poor quality, the electrodes were repositioned, one a time or the lead changed from II to I or III, until a good quality signal was obtained. Once a good signal was secured, vagal tone data collection was started by down-loading the ECG signal, via the one volt ECG output port connector, to a 486DX-100MHZ portable computer loaded with the Vgtone software program (developed by R. Powers MD, Children's Hospital Oakland CA, & L. Franck, PhD, RN). A 10 minute baseline heart rate for vagal tone, in two 5 minute epochs, was obtained.

The computer was reset to collect vagal tone data for 3 minutes: 1 minute prior to and 2 minutes during the intervention phase. The Sony CCDTR83 camcorder, placed on a tripod 4 feet from the foot of the bassinet, was positioned and focused to include the total baby, minimizing the amount of background viewed. The investigator verified that the camcorder had the time, in seconds, superimposed on the picture. The camcorder was turned on and left filming until 3 minutes after pressure was released from the heel, or until the infant stopped crying if longer than 3 minutes.

The selected intervention, depending on group assignment, was then implemented for two minutes. Treatment groups were:

1) a mini-Mam 0-6 months orthodontic pacifier (Sassy), moistened with water, gently held in the infant's mouth (without initiating any other physical contact) during intervention, blood collection procedure, and post-procedure time;
2) a mini-Mam 0-6 months orthodontic pacifier (Sassy), moistened with water then dipped in a single serving sugar packet to coat, gently held in the infant's mouth (without initiating any other physical contact) during intervention, blood collection procedure, and post-procedure time;

3) 2 cc of a 12% sucrose solution administered via oral syringe into the side of the infant's mouth;

4) routine care, no intervention offered during heelstick.

Social interaction with infants in all 4 groups was the same: infants were not talked to or touched except by the lab technician as related to the blood drawing procedure.

After the 2 minute intervention, with the camcorder recording and vagal tone data being collected, the blood specimen was obtained. The blanket was partially removed, uncovering the infant's feet and the disposable diaper removed. The heel was cleaned with a Webcol alcohol pad using two swipes of the area. A Becton-Dickinson blue lancet was used to puncture the medial or lateral aspect of the plantar surface of the heel in order to obtain the blood specimen. The area was milked until an adequate blood sample was obtained. Additional lancing was performed if bleeding was insufficient, as consistent with routine blood sampling procedures. Pressure was applied to the site with a dry gaze until bleeding stopped, then a spot Band-aid applied.

The camcorder was turned off after 3 minutes or after the infant stopped crying. Heart rate monitoring for vagal tone was continued, in 5 minute segments, for 25 minutes. Twenty-five minutes after the initial heel lance was done, the post-procedure salivary sample was collected in the same manner as sample A and labelled as sample B.

If the infant was, in the opinion of the investigator, overly distressed in the post procedure data collection period then data collection would have been stopped and the infant swaddled, held, rocked, offered a pacifier, or otherwise comforted.

Data Collection Flow Diagram

- explain experiment to parents, obtain informed consent
- bring infant to nursery
- ensure that infant has clean diaper
- bring infant to quiet awake state
- place infant in bassinet on right side
- collect first cortisol sample
- place EKG leads
- apply warm, moistened diaper to left foot
- turn on EKG machine and adjust leads for clear signal
- collect baseline vagal tone (two 5 minute epochs)
- reset computer for intervention vagal tone collection (3 minute epoch)
- turn on camcorder
- perform appropriate intervention for 2 minutes
- reset computer for 5 minute vagal tone
- collect blood specimen
- turn off camcorder 3 minutes after procedure ends or when infant stops crying, if longer
- reset computer four times to collect vagal tone (four 5 minute epochs to total 20 minutes)
- turn off EKG machine
- collect post-procedure cortisol sample
- return infant to mother's room

Appendix E

Informed Consent to Participate in Medical Research

SADDLEBACK MEMORIAL MEDICAL CENTER

UNIVERSITY OF SAN DIEGO

INFORMED CONSENT TO PARTICIPATE IN MEDICAL RESEARCH

TITLE: "AN EVALUATION OF THE EFFICACY OF SELECTED NON-PHARMACOLOGIC PAIN INTERVENTIONS IN INFANTS"

P.I. David Lagrew, M.D. Phone: (714) 452-7199
Co-P.I./Contact Person Cindy Greenberg, DNS(c), RN, CPNP Phone: (714) 458-6634

PROJECT # 028-95(S)

I am being asked for my consent to have my infant participate in a research study conducted by Cindy Greenberg DNS(c), RN, CPNP under the supervision of David Lagrew, M.D. Ms. Greenberg is a registered nurse and a doctoral student at the University of San Diego. She is conducting this research as part of the requirements for completing her Doctor of Nursing Science degree.

The purpose of this study is to look at the effectiveness of various methods for pain relief in infants. This would be done when my baby has his/her blood drawn for the metabolic tests that are routinely done on all newborns (e.g., PKU, thyroid) before they go home from the hospital. My baby will be assigned to a group where he/she would either suck on a pacifier, suck on a pacifier coated with sugar, is given a sugar solution by mouth, or where routine care is given.

If I agree to have my baby participate, my baby will be taken to the nursery. I may accompany my baby, if I wish, but I will be asked to refrain from talking to or touching the baby while the study is being done. The study will take about an hour to complete. The procedure will be video taped to get information about crying.

A saliva sample will be obtained by having my baby suck on a cotton dental roll. If enough saliva is not obtained, 1 - 2 drops of a dilute citric acid solution will be given orally to stimulate salivation. There are few known side effects of dilute citric acid, it may potentially cause gagging, nausea, and/or vomiting.

My baby will then be connected to an EKG monitor that records heartbeat. EKG monitoring is not routinely done on newborn infants. There may be minimal, temporary redness of the skin at the site where the heartbeat monitor stickies were placed.

Depending on the group my baby is assigned to, one of the interventions will be done (pacifier, sugar, etc.). There are few known side effects of sucrose, it may potentially cause gagging, nausea, and/or vomiting.

The lab technician will then obtain the blood sample. After the blood sample is obtained, my baby will stay in the crib with the heartbeat monitor attached for 25 minutes until a second saliva sample is obtained. My baby will then be returned to my room.

Project # 028-95(S)
P.I. David Lagrew, M.D.
Contact Person Cindy Greenberg, DNS(c), RN, CPNP

My baby's participation in this study does not involve any additional risks or discomfort other than those involved in obtaining a the blood sample and those potential ones mentioned above regarding citric acid, sucrose, and EKG monitoring. My baby may benefit if any of the pain interventions are effective in relieving pain. Other infants may benefit in the future if effective pain interventions are identified from this research.

The research records of my baby will be kept completely confidential. To preserve anonymity, only coded or grouped data will be used in any publication of the results of this study.

All costs incurred by participation in the study (pre and post procedure salivary cortisol levels, electrocardiograph recordings, audiotapes) will be assumed by the investigator. Charges for the state-mandated newborn metabolic screening will be the responsibility of the parents. If my baby is injured as a result of research procedures which are the subject of this consent form, medical treatments will be available but will not be provided free of charge, nor will financial compensation be provided.

Participation in this study is entirely voluntary. I may refuse to have my baby participate or withdraw at any time without jeopardizing the care that I (or the baby's mother) or my baby will receive. There are no other agreements, written or verbal, related to this study beyond that expressed on this consent form.

Prior to signing this consent I was given an opportunity to have the study explained again and ask any questions that I had about my baby's participation. If questions arise in the future I may reach Cindy Greenberg at (714) 458-6634.

This proposal has been reviewed and approved by Long Beach Memorial Medical Center's Institutional Review Board (MHS Research Council), composed of physicians and lay persons, and by the University of San Diego's Committee on the Protection of Human Subjects. If I have any questions regarding the conduct of this study I can contact the Vice President, Office of Research Administration, Long Beach Memorial Medical Center, at (310) 490-3737.

I, the undersigned, understand the above explanations and, on that basis, give my voluntary consent for my infant to participate in this research. I have received a copy of this consent document, as well as a copy of the "Subject's Bill of Rights".

_____ _____

Signature of Parent/Guardian Date

_____

Location (e.g., Laguna Hills, CA)

_____

Signature of Co-Investigator

_____

Signature of Witness

RIGHTS OF HUMAN SUBJECTS IN MEDICAL RESEARCH

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.

4. Be given an explanation of any benefits to the subjects reasonably to be expected from the experiment.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of any signed and dated written consent form used in relation to the experiment.

10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

PATIENT STUDY NUMBER:_____ PATIENT SIGNATURE:_____

Appendix F

Demographic Characteristics of Sample

Characteristic	Water Pacifier	Sugar Pacifier	Oral Sucrose	No Intervention	Total Sample
Sex					
males	9	10	9	10	38 (45.2%)
females	12	11	12	11	46 (54.8%)
Ethnicity					
Caucasian	12	18	18	14	62 (73.8%)
Hispanic	2	1	3	3	9 (10.7%)
Black	2	1	0	1	4 (4.8%)
Other	5	1	0	3	9 (10.7%)
Age in hours	19.5	17.6	19.8	18.9	18.99
APGAR score					
1 minute	8.05	7.95	8.05	7.90	7.99
5 minute	9.04	9.00	8.95	8.90	8.98
Anesthesia					
none	0	1	2	3	6 (7.1%)
epidural	17	14	17	15	63 (75%)
spinal	2	1	2	2	7 (8.3%)
local	2	5	0	0	7 (8.3%)
epidural + spinal	0	0	0	1	1 (1.2%)
IV narcotics prior to delivery					
yes	2	5	1	1	9 (10.7%)
no	19	16	20	20	75 (89.3%)
Type of delivery					
vaginal	16	20	17	19	72 (85.7%)
planned Cesarean	3	0	4	2	9 (10.7%)
unplanned Cesarean	2	1	0	0	3 (3.6%)
Previous heelstick	1	0	2	2	5 (6%)

Characteristic	Water Pacifier	Sugar Pacifier	Oral Sucrose	No Intervention	Total Sample
Number of heel lances					
2	14	15	12	10	51 (60.7%)
3	3	4	7	4	18 (21.4%)
4	3	2	2	6	13 (15.5%)
5	1	0	0	0	1 (1.2%)
6	0	0	0	1	1 (1.2%)
History of circumcision	2	3	0	4	9 (10.7%)
Birth weight in grams					
mean	3329	3437	3484	3397	3412
SD	270.65	335.35	253.03	367.50	309.78
Gestational age in weeks	39.06	39.6	39.42	39.27	39.34
Time since last feeding in minutes	78	51	69	74	68
Procedure length in seconds					
mean	159	144	137	180	155
SD	49.79	29.00	25.64	62.13	46.57