A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL
EXAMINING THE ANALGESIC PROPERTIES OF
ORAL SUCROSE DURING ROUTINE IMMUNIZATIONS AT
TWO AND FOUR MONTHS OF AGE

A Thesis in
Nursing
by
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ABSTRACT

The purpose of this study is to evaluate the effectiveness of and age-related changes in analgesia of oral sucrose as a pre-procedural intervention for acute pain during routine immunizations at two and four months of age. Melzack and Wall’s (1965) gate control theory of pain served as the theoretical frame guiding this prospective, parent and investigator- masked, randomized, clinical trial. Forty healthy term infants receiving their routine two or 4-month immunizations at Penn State Milton S. Hershey Medical Center’s ambulatory pediatric clinic were sampled. Infants were randomized to the treatment group (24% sucrose, n=20) or the control group (sterile water, n=20). Infants’ study participation was at their two and four-month well-child visit. Treatment intervention was administered two minutes before the three serial routine immunizations. The University of Wisconsin Children’s Hospital pain scale measured infant behavioral pain response for the treatment and control group at baseline, two, and five minutes following solution administration. A two by two repeated measures ANOVA examined the effects of treatment conditions and age on pain assessment scores.

Comparisons of change in behavioral pain response between two and four months of age were not statistically significant at two minutes and five minutes following treatment administration (p-value=1.00). Age groups were combined within treatment, to test for a difference in change in behavioral pain response between treatment and control groups at two minutes and five minutes following treatment administration. Change in pain response from baseline to two minutes following treatment administration was not statistically significant (p-value=0.958). Between the treatment and control group the change in behavioral pain response from baseline to five minutes following treatment administration was statistically significant (p<0.0001). The effect of gender (p=0.1865), nutrition (p=0.8096), prior painful experiences (p=0.2159) and analgesia (p=0.2266) on behavioral pain response were statistically non-significant.

Immunizations constitute a necessary preventive health measure in pediatric clinics. Since healthy newborns’ behavioral pain response is increased after immunizations, it is reasonable to develop practical clinical interventions to promote comfort and alleviate their pain and distress. Sucrose is an effective pre-procedure intervention for decreasing behavior pain response after immunizations at two and four months of age.
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Epigraph

“In the case of infants, everything must depend upon the accurate observation of the nurse or mother who has to report.”

Nightingale, 1859, p. 63.
Painful experiences due to procedures during the first months of life may be a recent phenomenon, unforeseen by evolution. Since the risk of exposure to painful trauma in the newborn period should be minimal for small infants during the early stages of development, the raison d'ètre that pain-modulating mechanisms are immature at birth may be attributed to an evolutionary phenomenon. Human babies remain dependent on their mothers for a comparatively long time and are protected from painful trauma by close physical contact with the mother. Evidence in animal studies suggests pain and stress suffered in newborn animals program the brain with long-term consequences for behavior and later perceptions of pain apparent even in adult age (Fitzgerald, Shaw, & Mcintosh, 1988). The long-term consequences of pain and stress in infants are unknown. Clinical observations of newborn rat pups suggest that exposure to pain in early infancy can alter later perceptions of pain (Anand, Coskun, Thrivikraman, Nemeroff, & Poltsky, 1999; Anand & Scalzo, 2000). Winberg (1998, p. 723) proposes the long-term findings at follow-up that “exposure to contexts and contingencies that are evolutionary unexpected may…create pathology”.

Statement of Problem

The belief that infants are incapable of pain sensation and perception has persisted for many years (Anand et al., 1999; Bhutta & Anand, 2002; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; De Lima, Alvares, Hatch, & Fitzgerald, 1999; Fitzgerald, 1985; Fitzgerald, Woolf, & Shortland, 1990; Grunau, 2002; Grunau, Whitfield, & Petrie,
1994b; Shortland & Fitzgerald, 1994). This belief persisted through misconceptions about the infant’s response capabilities, misunderstanding of pain transmission mechanisms and uncertainty about the infant’s ability for memory of pain (Anand & Hickey, 1987). Recent evidence has substantiated that term and preterm infants have the anatomic and functional capacity for mounting a response to a noxious stimulus and for perceiving pain at birth (Anand & Carr, 1989; Anand & Hickey, 1987; Andrews & Fitzgerald, 1994; Coskun & Anand, 2000; Fitzgerald, 1991a).

Assessment of pain in infants is particularly challenging because physiologic and behavioral expressions of pain are more variable and less vigorous in younger infants than in older infants and young children. The sympathetic nervous system activates physiologic factors such as heart rate, respiratory rate and oxygenation in response to pain (Craig & Dostrovsky, 1999; Craig & Grunau, 1993; Craig, Prkachin, & Granau, 1992); however, these physiologic factors are more clearly associated with stress than pain and are not useful as the sole indicators of pain. The presence of facial expressions (brow bulge, eye squeeze, nasolabial furrow, raised cheeks, square mouth) are significantly greater in painful situations than in pain-free situations (Craig et al., 1992) and are present in infants as early as twenty-eight weeks’ gestation. Stevens and Franck (1995) found facial actions to be the most consistent behavioral indicators of pain across the age groups.

Alterations in normal neural activity patterns during early development can permanently alter the future pattern of connections within the central nervous system (Alvares, Torsney, Beland, Reynolds, & Fitzgerald, 2000). While this is well established in the auditory or visual system (Fitzgerald, 1991a; Volpe, 2000), it is not clear whether
aberrant sensory activity resulting from pain and injury during a critical period of early life will have long-term consequences upon somatosensory function (Alvares et al.; Volpe, 2000). There are reports of prolonged sensory disturbances and altered pain responses lasting well beyond the infant period in children who have undergone early pain and trauma (Porter, Grunau, & Anand, 1999). Neonatal circumcision which is unprotected from pain results in increased pain behavior three months later (Taddio, Goldbach, Ipp, Stevens, & Koren, 1995; Taddio, Katz, Ilersich, & Koren, 1997), while painful procedures performed in the neonatal intensive care unit may lead to complex changes in pain perception and somatization (Grunau, Whitfield et al., 1994b). Evidence suggests increased somatization at age of 4 ½ years in a population of extremely low birth rate infants (ELBW) experiencing repeated medical procedures in the NICU (Grunau, Whitfield et al., 1994b).

Adverse physiologic consequences occurring with pain (alterations in blood pressure and glucose) may be significant enough to influence the development of intraventricular hemorrhage in some infants (Volpe, 2000). Repeated or prolonged pain may deplete the infant’s stress hormones and result in the absence of any observable behavioral or physical response to pain. Moreover, the energy required for maintaining heart rate, blood pressure and oxygenation during repeated or long-term pain depletes resources necessary for growth and tissue repair (Anand & Scalzo, 2000).

In addition to adverse physiologic consequences, under-treated pain has short and long-term cognitive and behavioral consequences for infants (Anand & Hickey, 1987). Short-term effects may include disturbances in feeding, parent-infant interaction dysfunction, and alteration in sleep-wake cycles persisting long after termination of
noxious stimuli. Long-term effects include impairment of neurodevelopment, learning, memory (Sandkuhler, 2000), behavior (Carlson, Clement, & Nash, 1996) and increased somatization in childhood (Grunau, Whitfield et al., 1994b).

Over the past ten years, great progress has occurred in the treatment of acute and chronic medical and surgical pain in children. The use of opioid and non-opioid analgesics, local anesthetics, and regional anesthetic techniques in the treatment of pediatric pain has become commonplace (Maxwell & Yaster, 1996). Procedure-related pain, which children suffer during their medical or surgical treatment, has remained a vexing problem.

Because it is unethical to inflict pain intentionally on an infant for the sake of a study, researchers have used an alternative methodology to study acute pain in this population: naturalistic observation of infants undergoing painful procedures in the course of routine medical care. While necessary to promote health, multiple injections during routine immunization and the traditional practice of physical restraint creates pain and distress for many infants. The 1983 United States immunization schedule for infants and toddlers (up to twenty-four months) included five injections and four sets of oral drops to protect the children against seven infectious diseases: pertussis, tetanus, measles, mumps, rubella and polio (Centers for Disease Control and Prevention, 1983). The current 2006 immunization schedule requires infants and toddlers to receive twenty injections to prevent eleven infectious diseases. In addition to the seven immunizations children received in 1983, immunizations against pneumococcus, hepatitis B, haemophilus influenzae and varicella have been added (Centers for Disease Control and Prevention, 2002). Whereas the 1983 schedule called for only one injection at each visit
in the first two years of life, the current schedule calls for as many as five injections at each visit; therefore, routine immunizations provide an ideal paradigm for the study of procedural pain in infants.

Parents perceive that their infants endure a substantial amount of pain during routine immunizations: almost twice the amount they hypothesize an adult undergoing a similar injection would experience (Pillai, Badali, & Craig, 2004). If parents perceive pain as a barrier to immunization, it may provide one explanation to parental non-compliance with the recommended immunization schedule. Gellin, Maibach and Marcuse’s (2000) telephone survey revealed 75% of parents were concerned their infants received too many painful vaccines in one office visit. Woodin et al. (1995) found parental concern about their infant’s pain correlated with the number of injections their infant received. Thirty-one percent of the parents whose infant received one injection expressed strong concern about immunizations while 41% of parents whose infant received three simultaneous injections expressed strong concern.

An ideal analgesic for healthy young infants during immunizations would be a short-acting agent with few adverse affects. It should be cost-effective and provide significantly greater analgesia than the current standard of care. To date, no such agent exists to challenge the current standard of care, which is to administer no analgesia. Moreover, healthy young infants have limited therapeutic alternatives for immunization pain. Opioid analgesics are not therapeutically indicated for minor procedural pain such as immunizations. Codeine, a weak opioid, is effective for minor procedural pain; however, it requires conversion by CYP2D6 to its active component, morphine.
Compared to adults, less than 10 percent of infants under two months of age are capable of this conversion (Masters-Harte & Abdel-Rahman, 2001).

The efficacy of a single dose of sucrose for the relief of procedural pain in preterm and term infants is well documented (Barr et al., 1994; Blass & Ciaramitaro, 1994; Blass, Fitzgerald, & Kehoe, 1987; Gunnar, Connors, Isensee, & Wall, 1988; Stevens & Ohlsson, 1998; Stevens, Yamada, & Ohlsson, 2001b, 2004). Oral sucrose has been examined for its ability to calm and relax crying term newborns (Barr et al., 1994) and its analgesic effects for invasive procedures in term and preterm infants (Stevens & Ohlsson, 1998; Stevens et al., 2001b). Stevens et al. found the most efficacious treatment for reducing procedural pain in infants born at thirty-two to thirty-four weeks’ gestation was combining a single dose of 24% sucrose with non-nutritive sucking (NNS) via a pacifier.

Oral sucrose has shown promise in minimizing pain in infants (Stevens, Yamada et al., 2004), but little research has been conducted beyond the neonatal period, and contradictory reports hamper the ability to draw definitive conclusions. The absence of a clear definition of pain or a valid means to measure pain intensity contributes to conceptual and methodological limitations. Previous studies considered proportion, percentage, or duration of crying to be the most valid indicator of pain in infants (Lewindon, Harkness, & Lewindon, 1998; Ramenghi et al., 2002). Recent research suggests that a multivariate approach or a composite pain score including physiologic, behavioral, and contextual indices is a more valid measure of pain in infants (Johnston, Stremler, Horton, & Freeman, 1999). Limitations of previous studies are: 1) utilization of
heel lance as the pain stimulus, 2) variable sucrose concentrations, dose, and delivery methods and 3) soothing interventions throughout the procedure.

Purpose of the Study

Efforts to minimize pain due to medical procedures during the first few months of life represent an important area of nursing research. The purpose of this randomized clinical trial was to investigate the analgesic effects of oral sucrose (1) as a pre-procedural intervention prior to routine immunizations in infants at two and four months of age and (2) to assess the age-related changes in analgesia over time. The proposed plan of study evaluated the analgesic effects of clinically established concentrations of oral sucrose during routine immunization injections in healthy, full-term infants at two and four months of age. The systematic study and development of practical clinical interventions for pain management during immunizations offers an alternative approach to promote comfort and alleviate pain and distress in healthy newborns for other medical procedures.

Conceptual Framework

There is sufficient evidence to support the infant's anatomical and functional capacity to respond to pain (Anand & Carr, 1989; Anand & Hickey, 1987; Andrews & Fitzgerald, 1994; Coskun & Anand, 2000; Fitzgerald, 1991a). Since preterm and term neonates have functioning afferent nerve fibers by early gestation, inhibiting afferent nerve fibers stimulation may control pain during procedures. Similarly, interventions that promote inhibitory mechanisms in preterm infants who lack sufficiently developed
inhibitory mechanisms (via endogenous opioid and non-opioid pathways) may modulate pain responses.

*The Gate Control Theory of Pain*

The Gate Control Theory of Pain (GCTP) is a reappraisal of the specificity theory (Decartes, 1664; Von Frey, 1894) and pattern theory (Darwin, 1872; Fellous, 2005; Goldscheider, 1981) of pain. Building on a picture of a complex phenomenon, the Gate Control Theory of Pain explains human responses to noxious situations. The GCTP is a set of relationships derived from the basic principles of transduction, transmission and modulation. It is hierarchical in nature in that one stage is required before progression to the next stage (e.g., transmission cannot occur without transduction).

From a theoretical standpoint, pain is a complex multi-dimensional phenomenon that is dependent upon an individual’s description of a sensory and emotional experience associated with actual or potential damage (Melzack & Wall, 1965). This conceptualization of pain precludes pre-verbal infants who are unable to provide subjective reports. Nociception is a term that is used to describe the physiologic mechanisms (metabolic and neurobehavioral) in the presence of a noxious stimulus that is independent of any judgment of higher consciousness, memory, emotional effects or suffering. Anand and Hickey (1987) offer an alternative perspective and postulate that nociceptive activity rather than pain should be discussed with regard to the infant because pain is a sensation with strong cognitive and emotional associations. The focus on pain perception in infants and the confusion over its differentiation from nociceptive activity and the accompanying behavior and physiologic responses have obscured the mounting evidence that nociception is important in the biology of infants. This is true, regardless of
any philosophical view of consciousness and pain perception in newborns (Anand & Hickey, 1987). In pediatric literature, terms relating to pain and nociception are used interchangeably.

Melzack and Wall (1965) propose that pain is a subjective, multi-dimensional, linguistic label for a rich variety of experiences and responses. It represents an abstraction for the integration of sensory, affective and cognitive dimensions that are subsequently re-examined over long periods by the entire somesthetic system. According to the Gate Control Theory of Pain which focuses on nociceptive activity, responses to pain are influenced by internal pain inhibitory mechanisms and external factors such as an individual’s memories of past painful experiences, culture, or expectations of pain (Fields & Basbaum, 1994; Melzack & Wall, 1996; Wall, 1996). Pain responses are flexible, and influenced by a variety of contextual factors that further account for the differences in pain responses among and within individuals (Fields & Basbaum, 1994).

The GCTP (Melzack & Wall, 1965, 1970, 1996; Wall, 1996), Figure 1, hypothesizes that pain is a function of the balance between the information traveling into the spinal cord through large Aβ nerve fibers and information traveling into the spinal cord through small Aδ and C nerve fibers. Large Aβ nerve fibers carry non-nociceptive information and small Aδ and C nerve fibers carry nociceptive information. If the relative amount of activity is greater in large nerve fibers, there should be little or no pain; however, if there is more activity in small nerve fibers, then there will be pain. The substantia gelatinosa in the dorsal horn of the spinal cord consists of densely packed
Figure 1: Gate Control Theory of Pain. Excitatory (white circle) and inhibitory (black circle) form links from substantia gelatinosa (SG) to transmission (T) cells as well as descending inhibitory control from brainstem systems. Round knob at end of inhibitory link implies its action may be presynaptic, postsynaptic, or both. All connections are excitatory except the inhibitory link from SG to T cells.

interneurons that extend the length of the spinal cord and act as a gate control system that modulates the synaptic transmission of nerve impulses from peripheral fibers.

Without noxious stimulation, both large and small nerve fibers are quiet and the inhibitory interneurons in the substantia gelatinosa (SG) block the signal in the transmission cells (T) that transfer information to the brain. The gate, (transmission cell) is closed and pain is not perceived.

With non-painful stimulation, large $\text{A}\beta$ nerve fibers are activated primarily. This not only activates the transmission cells (T), but also activates the inhibitory interneurons in the substantia gelatinosa (SG). This blocks the signal in the transmission cells (T) that connects to the brain. The gate, (transmission cell) is closed and pain is not perceived.

With the transmission of noxious stimuli from afferent $\text{A}\delta$ and $\text{C}$ fibers, small nerve fibers become active. They activate the spinal cord transmission cells (T) and concurrently block the inhibitory interneurons in the substantia gelatinosa (SG). Because activity of the inhibitory interneurons in the substantia gelatinosa (SG) is already blocked, it cannot block the output of the spinal cord transmission cells (T) that transmit the information to the brain. The "gate is open", noxious stimuli are transmitted to the brain and the individual may perceive pain.

The spinal gating mechanism can be influenced by nerve impulses that descend from the brain. Modulation of impulses involves the active transformation of impulses from primary neurons (peripheral fibers) to secondary neurons. A specialized system of large diameter, rapidly conducting $\text{A}\beta$ fibers activate selective cognitive processes that influence, by the way of descending fibers, the “gating mechanism” to increase or decrease the flow of nerve impulses at the level of the spinal cord.
Pain impulses involve transduction of nociceptive impulses from peripheral receptors via ascending afferent fibers, transmission of nociceptive impulses to the spinal cord and the brain, perception of the stimulus, and modulation of the stimulus by descending inhibitory pathways (Melzack & Wall, 1996; Scholz & Woolf, 2002). When the output of the spinal cord transmission (T) cells exceeds a critical level, it activates the action system. The action system is comprised of neural areas that underlie the complex, sequential patterns of behavioral and physiological characteristics of pain. A pain response occurs when neural mechanisms are exceeded or inhibitory mechanisms are ineffective (Wall, 1996). Interventions that compete with small diameter afferent fibers to close the gate, or activate descending endogenous opioid and non–opioid pathways to decrease nociceptive transmission, are thought to decrease pain. Since preterm and term neonates have sufficient afferent fibers by early gestation, control of pain during procedures may be achieved by providing large rapidly conducting Aβ fiber stimulation. Similarly, interventions that promote inhibitory mechanisms in infants who lack sufficiently developed inhibitory mechanisms (via endogenous opioid and non-opioid pathways), may modulate pain responses (Fitzgerald, 1991a, 1991b, 1993).

The Gate Control Theory of Pain offers a theoretical framework to examine pain and pain-relieving interventions in infants; however, further examination of the developmental differences between term and older infants is required. Since pain is a subjective, multi-dimensional experience, influenced by developmental, environmental and contextual factors (Melzack & Wall, 1996) multiple methods of pain assessment are required. Interventions effective in older children and adolescents may not be effective for younger infants. Examination of the plasticity of the developing central nervous
system in young infants in response to noxious stimuli will offer a comprehensive conceptualization of pain.

Summary of Conceptual Framework

Melzack and Wall’s (1965) conceptualization of the modulation of noxious stimulation is hypothesized to function at two separate levels: (1) the flow of nociceptive impulses via the afferent fibers (Aδ and C fibers) and (2) the release of inhibitory neurotransmitters, endogenous opioids and increased serotonin uptake from the descending pathways at the level of the spinal cord. The Gate Control Theory of Pain states that nerve impulses evoked by injury are influenced in the spinal cord by nerve cells that act like gates, either preventing the impulses from getting through or facilitating their passage. The theory accepts the brain as an active system that filters, selects and modulates inputs. The dorsal horns are not passive transmission stations but sites where the dynamic activities of inhibition, excitation and modulation occur.

Research Questions

This study asked the following research questions to test the study hypotheses:

Primary Research Question

Will sucrose decrease behavioral pain response during routine immunizations in an infant at the two and four month well-child visit?
**Second Research Question**

After sucrose administration, will there be age related change in behavioral pain response during routine immunizations in an infant at the two and four month well-child visit?

**Hypothesis**

_Hypothesis: Primary Research Question_

In infants two and four months in age, a 24% intra-oral sucrose solution, 0.6 ml/kg (0.3ml/lb) and non-nutritive sucking will significantly decrease the objective measures of acute pain during three serial routine immunizations compared to a volume-equivalent dose of a sterile water control solution and non-nutritive sucking.

_Hypothesis: Second Research Question_

In infants two and four months in age, using a 24% intra oral sucrose solution, 0.6 ml/kg (0.3ml/lb) and non-nutritive sucking, there will not be an age-related change in analgesia during routine immunizations at the two-month and four-month appointment compared to a volume-equivalent dose of a sterile water control solution and non-nutritive sucking.

**Definitions**

For manuscript clarification, the following terms are defined:

*Analgesia*

A neurologic or pharmacologic state in which painful stimuli are moderated that, though still perceived, are no longer painful (Anderson, 1994a).
**Intraoral Sucrose**

Sucrose is a non-reducing disaccharide obtained from cane sugar, sugar beet and sorghum. It is composed of glucose and fructose linked via their anomeric carbons. It is used extensively as a food and sweetener (Anderson, 1994b). Sucrose is defined as a 24% disaccharide solution manufactured by Children's Medical Ventures Inc., Norwell, MA.

**Non-Nutritive Sucking**

An infant displays non-nutritive sucking (NNS) when a nipple is placed in the mouth without the presentation of breast milk or formula. In contrast to the long, continuous, rhythmic pattern characteristic of nutritive sucking, non-nutritive sucking has a pattern of shorter, alternating bursts of sucking and rest (Blackburn & Vanderberg, 1998).

**Noxious Stimuli**

Noxious stimulation is used by an organism to make it aware of stimuli of an intensity that could potentially or actually cause damage to body tissues (Turk & Okifuji, 2001). For the purposes of this study, routine immunizations, administered at two and four months of age, will be the noxious stimuli.

**Pain**

An unpleasant subjective sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (International Association for the Study of Pain Subcommittee on Taxonomy, 1979). The inability to communicate in no way negates the possibility that an individual is experiencing pain (International Association for the Study of Pain Subcommittee on Taxonomy, 2001). The mean score on the University of Wisconsin Children's Hospital Pain Scale (UWCH)
(Soetenga, Frank, & Pellino, 1999) will be used to define and measure infant pain 
(Appendix A).

Assumptions

The following assumptions guided this study:

(1) All infants have the anatomical and functional capacity to transmit noxious 
stimuli at birth.

(2) Anything that causes pain in adults is also capable of causing pain in infants.

(3) Some interventions that are not painful to adults may cause pain in infants.

(4) Pain assessment encompasses responses during and after a noxious stimulus 
occurs.

(5) Infants can respond to pain with a variety of physiologic and behavioral 
indicators, but they may also exhibit no observable responses.

(6) An absence of an observable pain response does not confirm absence of pain.

(7) In infants, multiple indicators are necessary for pain assessment. Changes in 
these indicators are significant.

(8) Parents and caretakers familiar with the infant are valid and reliable sources of 
pain information in infants.

Significance

This study provided a unique contribution to the efficacy of intra-oral sucrose as a 
pre-procedural analgesic for infants at two and four months of age. Findings from this 
study made significant contributions toward nursing practice, theory and education. The
significance of this study is addressed in three sections. The first section presents the significance for clinical practice. The second section addresses the development of a theoretical model and the final section offers directions for future education and research.

*Significance for Clinical Practice*

Intramuscular injections in early life may be partly responsible for the fear of injection which many people maintain in adult life, and is one of the reasons for their reluctance to donate blood (Fassler, 1985; French, Painter, & Coury, 1994). Nurses are responsible for providing direct care to infants and are most often the individuals administering the immunization. Although pain management for infants has improved over the last few decades, many painful procedures such as routine immunizations continue to be performed on infants without appropriate analgesia or comfort measures. This sub-optimal management of procedural pain is related to misconceptions of infants' capacity to detect, transmit and interpret pain as well as concerns about the clinical toxicity of analgesics. The pharmacokinetics (movement of drugs in the body over time) and pharmacodynamics (dose-response relationship) of an analgesic agent must be considered carefully before it is administered to an infant (Stevens et al., 2001b). In addition, the developmental and metabolic functions of younger infants must be considered prior to the administration of analgesics. Due to the increase in the number of immunizations and the concerns over the effects of analgesics, it may neither be safe nor feasible to administer analgesics at every clinic visit; therefore, alternative approaches that are safe and efficacious are required.

Sucrose and NNS are readily available in pediatric clinics, and are inexpensive, easily administered and safe. Given the rapid and enduring effects of sucrose and NNS,
they can be given together in advance of mild to moderate procedural pain. Although sucrose and NNS is not efficacious for moderate to severe pain, the combined therapy may be useful as an adjunct with pharmacological interventions. Nursing knowledge acquired from this study will maximize analgesic effect of painful procedures, reduce the exposure of infants to analgesic and anesthetic agents, reduce the risk of infant morbidity and mortality, and prevent adverse neonatal brain development and behavior changes associated with painful exposures early in life.

Significance to Nursing Theory

The conceptual model for this study proposes that pain is not a simple process, but rather, one that involves transduction, transmission, modulation, and perception of nociceptive impulses within a developing central nervous system. Based on the GCTP, an understanding of neuroanatomy, neurophysiology, and factors that influence pain response, it is hypothesized that sucrose and NNS would be an efficacious pre-procedural intervention to diminish pain responses in infants at two and four-months in age during routine immunizations.

The data from this study describing infants’ responses to painful procedures will contribute to the multi-dimensionality of pain in this population and support the proposal that young infants’ complex responses to painful procedures can be reduced with the administration of sucrose and NNS. These data will form the basis for a conceptual framework on which to examine the efficacy of sucrose and NNS with other environmental, behavioral, or pharmacological interventions.
Significance for Education

Despite the evidence that sucrose and NNS is a safe intervention to reduce procedural pain in infants at thirty-four to forty-two weeks’ gestation (Stevens, Taddio, Ohlsson, & Einarson, 1997; Stevens & Ohlsson, 1998; Stevens et al., 2001b; Stevens, Yamada et al., 2004), changes in pain management practices will not occur until health care providers recognize (1) the existence of infant pain, (2) the physiological and behavioral indicators of infant pain and (3) the immediate and long-term consequences of pain experienced in early infancy. Findings from this study will provide a forum to challenge existing practices and make evidence-based recommendations towards implementing new pain management practices.

Chapter Summary

Although adults are expected to tolerate painful interventions as part of their medical care, children are generally unable to balance a current or anticipated pain against the future benefit of medical treatment (Finley, 2001). In the developed world, immunizations are the most common painful intervention performed on infants. Despite the increased focus on infant pain assessment and management, mounting evidence suggests young infants’ neurodevelopmental outcomes remain a cause for concern. Cumulative brain damage during infancy may ultimately lead to reductions in brain volume, abnormal behavioral and neuroendocrine regulation, poor cognitive outcomes and altered pain responses in childhood and adolescents (Bhutta et al., 2002). Increasing evidence supports the adverse long-term neurological sequela of repeated painful procedures unprotected from pain (Alvares et al., 2000; Anand et al., 1999; Bhutta &
Infant pain management has been less than optimal. Even when their pain was obvious, infants frequently received inadequate or no treatment for pain or painful procedures. The “common wisdom” that infants do not respond to painful stimuli or do not remember painful experiences is simply untrue (Maxwell & Yaster, 1996). Evidence supports the infant's ability to mount a response to noxious stimuli (Anand & Carr, 1989; Anand & Hickey, 1987; Coskun & Anand, 2000; Fitzgerald, 1991b) and the utilization of opioids and sucrose to diminish mild to moderate procedural pain in preterm and term infants (Stevens et al., 2001b). Repeated studies in older children and adults provide evidence that the failure to give adequate analgesia to patients in pain increases morbidity, medical costs, and the duration and intensity of illness (Maxwell & Yaster).

Now recognized as unacceptable, the time-honored technique of immobilization by physical restraint was carried out only because infants could not verbalize their pain, were unable to withdraw consent, and were easily overpowered.

The public health and economic importance of preventing or ameliorating the possible subtle brain damage and increased pain sensitivity caused by infant pain cannot be overestimated. The concerted efforts by medical professionals to investigate the mechanism underlying early neuronal activity, to minimize the impact of adverse experiences and environmental factors in newborns, and to develop novel therapeutic strategies for improving the cognitive and behavioral outcomes of infants requires no
further justification. Immunization injections are a necessary preventive health measure in pediatric offices and clinics; therefore, the systematic study and development of practical clinical interventions for pain management during immunizations is important. Although pain during heel lancing and venipuncture has received considerable attention, immunization injections occur far more frequently. Pain management during injections has implications for a far wider population of infants independent of race, religion, social economic status, or gender. The direction of pain management research for infants and young children should identify a reasonable means of mitigating procedural pain. Sucrose may be a feasible pre-procedural intervention for analgesia in infants.
CHAPTER 2

REVIEW OF THE LITERATURE AND CONCEPTUAL FRAMEWORK

The purposes of this review are three-fold: (1) to provide a description of infant pain physiology, including the gestational ages during which physiologic maturation makes a difference in the physiology, (2) to describe infant's responses to pain, and (3) to identify the consequences of repeated painful experiences for infants. The goals of pain management in nursing are to prevent pain and to reduce the perception of pain by using pharmacologic and/or behavioral and environmental interventions. Research relevant to the management of procedural pain in infants will be discussed. A better understanding of the infant's pain and stress responses that are correlated to the infant's unique neuroanatomy and neurochemistry will provide the rationale for the pain-relieving interventions for procedural pain management that are both successful and non-detrimental to neuroanatomic development in infants.

Standard search methods were carried out for relevant peer-referred articles published from MEDLINE January 1966-December 1, 2005, CINHAL, January 1966-December 1, 2005, and the Cochrane Library, Issue 4, April 2005. Keywords and MeSH terms were analgesia, infant, neonatal, newborn, nociception, pain, sucrose, and immunizations. Language restrictions were imposed and limited to English. Bibliographies, personal files and communications, recent relevant neonatal, pediatric and pain journals, and recent major adult and pediatric pain conference proceedings were searched manually. Unpublished studies and dissertations were included.
Definition of Pain

The belief that infants do not experience pain has been successfully challenged. A substantial body of anatomical and physiologic evidence supports the infant's capacity to respond non-verbally to tissue-damaging stimuli at birth, even if the infant is preterm (Anand et al., 1999; Anand & Hickey, 1992; Bhutta & Anand, 2002; Bhutta et al., 2002; De Lima et al., 1999; Fitzgerald, 1985; Fitzgerald et al., 1990; Grunau, 2002; Grunau, Whitfield, Petrie, & Fryer, 1994; Shortland & Fitzgerald, 1994). In the past, the controversy surrounding infant pain and its management resulted in part from health care providers’ personal practices, traditions, and the lack of a valid and reliable method to assess and measure infant pain.

The first step in comprehending infant pain is to define and clarify common terminology. Stress is a term applied to the physiologic responses generated by endogenous or exogenous stimuli (Coleman, Solarin, & Smith, 2002; Lazarus, 1999). Distress is the suffering that results from excessive stress or maladaptive stress responses (Coleman et al.). The terms stress, distress and pain are often used interchangeably. Recognition of stress and distress by the patient is thought to require higher consciousness, and is often affected by experience. Recognition of stress and distress by an observer depends on either a verbal description or the inference of suffering from behavior and physiologic cues (Coleman et al.).

In 1979, the International Association for the Study of Pain (IASP) defined pain as:

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is always
subjective. Each individual learns the application of the word through experiences related to injury in early life (p. 250).

Implicit in this definition of pain are two components: a neurophysiologically determined sensory component and an emotional component based on an affective state, past experiences, development, and a variety of other factors. Significant to the understanding of pain is the knowledge that pain is an individual experience and not necessarily linearly related to the amount of tissue damage that has been incurred. Pain is a composite of the nociceptive stimulation from the tissue damage plus a host of modifying factors that might diminish or magnify the pain. Knowledge of the fundamental subjectivity of pain is essential to understanding its under-treatment (Schechter, 1989).

Application of the IASP definition of pain and its components to pre-verbal infants is unfortunate since infants are incapable of self-report and may not have encountered prior noxious events. Therefore, in 2001, the IASP added this note to the definition of pain: “The inability to communicate in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment” (p. 2). This addition is pertinent for infants and other individuals with limited ability to communicate pain robustly due to immaturity or severe medical illness.

Elements of Pain Perception

Pain is a perception, not a sensation. It involves sensitivity to chemical changes in the tissues and interpretation that such changes are harmful. This perception is real, whether the harm has occurred or is occurring. Cognition is involved in the formation of
this perception. There are emotional consequences and behavioral responses to the
cognitive and emotional aspects of pain (Melzack & Wall, 1965).

Pain responses are integral components of an adaptive biologic system that enables a newborn to function in a dynamic, challenging, and potentially dangerous environment. These responses represent reactions, modulations, and integration by the peripheral nervous system (somatosensory, somatomotor, autonomic), spinal cord, and brain (brain stem, medulla, hypothalamus, thalamus, limbic system, cranial nerves, and the neocortex). Taken together, the responses essentially are concurrent reactions of pain perception, an experience of emotions and autonomic, somatomotor and endocrine responses rather than sequential reactions (Janig, 1995). This description of concurrent responses to pain and stress is a very important differentiation from the pain-response physiology discussed to date. Melzack (1982) expanded the Gate Control Theory of Pain to consider the assertion that organisms respond to and communicate pain simultaneously in several different areas, using more than just the ascending and descending pain pathways for communication.

Pain is a linguistic description for an expansive variety of experiences and responses. It is an abstract representation of the information that is subsequently re-examined over long periods by the entire somesthetic system (Melzack & Wall, 1965). The physiologic mechanisms involved in the phenomenon of pain are known as nociception. The term nociception refers to the ability of a nerve to detect noxious stimuli and transmit the information concerning the stimuli to the brain for interpretation (Mcgrath, 1993). Unlike the phenomenon pain, nociception does not require self-report.
Therefore, the term nociception provides an accurate description of an infant's response to a tissue-damaging stimulus.

*Nociception*

The function of nociception is to provide information about a stimulus and to elicit a response from specialized fibers that indicate the location and intensity of the stimulus. Nociceptive neurons are sensitive to thermal, mechanical or chemical noxious stimuli. They contain and release neuropeptides and are sensitive to particular growth hormones involved in neurogenic inflammation (e.g. vasodilation, vascular leakage) and neuroimmune regulation. Nociceptive neurons also influence smooth muscle contractions and glandular secretion into the gastrointestinal and urinary tracts (Anand & Carr, 1989).

The basic processes of nociception are:

1. Local peripheral nervous system reactions or transduction occurs when noxious stimuli are translated into neuronal action potential at the nociceptors, which are the sensory endings of the primary afferent neurons in the periphery.

2. Spinal cord processing, referred to as transmission and modulation, is the propagation of action potentials along ascending pathways from the site of transduction throughout the sensory nervous system to the spinal cord, then centrally to the brain; and activation of descending pathways that exert inhibitory effects on the synaptic transmission of noxious stimuli.

4. Plasticity refers to localized inflammation during early infancy that permanently alters neuronal circuits that process pain in the spinal cord (Anand, 2000b; Ruda, Ling, Hohmann, Peng, & Tachibana, 2000).

The discussion is presented sequentially for clarity; however, events are concurrent.

Local Peripheral Nervous System Reactions: Transduction

The peripheral nervous system is fully mature and functional in the developing preterm. By twenty weeks of gestation, the peripheral nervous system consists of A\(\delta\), A\(\beta\), and C neuronal afferent fibers in the skin and mucous membranes. The number of nociceptors in a twenty-week preterm infant is equal to or greater in density than that found in adult skin (Anand, 2000a). Chemical responsiveness of these nociceptors in the human newborn remains uncertain.

The nociceptive pathway begins with a noxious stimulus that is detected by nociceptors in the primary afferent neurons. Local tissue injury, such as immunization, triggers several levels of responses. The immediate response is for nociceptors to transduce noxious stimuli into action potentials that flow centrally to the spinal cord and brain by means of the axon potential of first order neurons. Two types of fibers are responsible for the transmission of noxious stimuli from the site of injury to the spinal cord: small diameter, myelinated A\(\delta\) fibers and unmyelinated C fibers. A-\(\delta\) fibers are faster-conducting fibers that transmit defined, sharp, pain in \(5.9 \pm 0.8\) m/sec meters per second. C fibers are slow conduction fibers that transmit poorly localized, dull, aching pain. C fibers respond to mechanical, thermal and chemical stimulation at approximately \(0.6 \pm 0.1\) meters per second (Fitzgerald, 2000; Koga et al., 2005). The characteristics and functions of these fibers are summarized in Table 2.1.
The injury creates a cascade of chemical reactions that result in hyperalgesia of the surrounding tissue. The peripheral endings of nociceptors release neurotransmitters adenosine triphosphate, glutamate, neurokinin A and substance P that affect signal generation and excite or inhibit the nerve endings. These neurotransmitters create a composite picture of tissue conditions via the patterns and volume of signals that arrive at the dorsal root ganglion and the CNS (Byers, 2001). Afferent Aδ and C fiber nociceptive neurons have a repertoire of function phenotypes that are stimulated by different tissue conditions. Thresholds, physiologic and pharmacologic properties differ for each phenotype permitting the CNS to receive different types of information based on tissue inflammation or injury (Carlton, 1998; Millan, 1999).

Cellular and blood vessel damage from injury cause a cascade of chemical reactions. Bradykinin, calcium and potassium ions, substance P, and prostaglandins activate or sensitize nociceptors of Aδ and C afferent fibers to transmit pain impulses to the spinal cord and stimulate local inflammatory flare and wheal responses that occur at a finite time after nerve transmission. Substance P increases the degree of inflammation and, along with prostaglandins, creates local primary hyperalgesia through nociceptor recruitment and mediates continued nociceptor sensitization. As with adults, the local pain threshold decreases, and touch stimulation of inflamed tissue activates pain sensations that continue long after the stimulus is removed (Fitzgerald, Millard, & Macintosh, 1988; Merskey & Bogduk, 1994). With repeated tissue damage, the extension of inflammation and tenderness into adjacent uninjured tissue causes pain sensations (allodynia) from stimuli that normally do not provoke pain sensations (Merskey & Bogduk). The local tissue damage from repeated heel sticks is associated with a
Table 2.1 Primary Afferent Fibers

<table>
<thead>
<tr>
<th>Fiber</th>
<th>Aβ</th>
<th>Aδ</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Thickly Myelinated</td>
<td>Thinly Myelinated</td>
<td>Unmyelinated</td>
</tr>
<tr>
<td>Source of Pain</td>
<td>Cutaneous pressure, Touch</td>
<td>Mechanoreceptive, Pressure,</td>
<td>Polymodal stimuli</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temperature</td>
<td>(mechanoreceptive, chemical,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>thermal)</td>
</tr>
<tr>
<td>Diameter</td>
<td>$6 - 12 \mu m$</td>
<td>$1 - 5 \mu m$</td>
<td>$0.2 - 1.5 \mu m$</td>
</tr>
<tr>
<td>Conduction Velocity</td>
<td>$19.6 \pm 1.3 \text{ m/sec}$</td>
<td>$5.9 \pm 0.8 \text{ m/sec}$</td>
<td>$0.6 \pm 0.1 \text{ m/sec}$</td>
</tr>
<tr>
<td>Threshold for Stimulus Intensity</td>
<td>$0.8 \pm 0.2 \text{ mA}$</td>
<td>$1.80 \pm 0.6 \text{ mA}$</td>
<td>$3.1 \pm 0.5 \text{ mA}$</td>
</tr>
<tr>
<td>Duration of Action Potential</td>
<td>$0.29 \pm 0.01 \text{ ms}$</td>
<td>$0.63 \pm 0.05 \text{ ms}$</td>
<td>$1.38 \pm 0.01 \text{ ms}$</td>
</tr>
<tr>
<td>Sensory quality of pain mediated</td>
<td>- Non-nociceptive; inhibits the effects of firing by Aδ and C fibers</td>
<td>- Sharp, stinging, cutting, pinching</td>
<td>- Dull, burning, aching</td>
</tr>
<tr>
<td></td>
<td>- Discriminative touch,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>perception of pressure,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>vibration, and texture</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Proprioception</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

heel (Fitzgerald, Millard et al., 1988). This lowered pain threshold (tenderness) persists for days and weeks increasing the infant’s pain sensations. In these infants, intense pain can be elicited from gentle touch near the injured area (Fitzgerald, 1999; Fitzgerald, Millard, & Mcintosh, 1989).

In addition, tissue damage in the early neonatal period causes profound and lasting dendritic sprouting in the local sensory nerve terminals. This dendritic sprouting results in hyperinnervation of the wounded area lasting into adulthood (Fitzgerald, 1985; Fitzgerald et al., 1990; Reynolds & Fitzgerald, 1995). Behavioral studies report a long-lasting hypersensitivity and lowered mechanical threshold in the injured area. A more pronounced sprouting response occurs when the injury occurs at birth or shortly thereafter. If the injury occurs when the infant is older, less sprouting occurs (Fitzgerald, 1999). Studies have not determined the duration of hypersensitivity and lower threshold in older infants.

**Spinal Cord Processing: Transmission**

The spinal cord functions independently in the developing infant’s immature nervous system. In an infant under forty-six to forty-eight weeks in age, immature descending pathways impede cortical control of pain. Tactile, as well as noxious or painful stimuli, evoke cutaneous limb withdrawal reflexes in infants as young as twenty-seven weeks of gestation (Andrews & Fitzgerald, 1994; Fitzgerald & Jennings, 1999; Fitzgerald, Shaw et al., 1988). Weak linkages between afferent fibers and dorsal horn cells in the first postnatal week of life permit a single stimulus to elicit pain responses that last several minutes, whereas other stimuli fail to cause a reaction (Fitzgerald, 1993, 1999, 2000). In newborns, the receptive fields of dorsal horn cells are larger than those
found in adults and gradually diminish in size during the first two weeks after birth (Fitzgerald, 1999). In young infants, therefore, behavioral response to pain is a manifestation of a series of spinal reflexes requiring time and experience to become integrated into the sophisticated behavior patterns of the adult spinal reflexes under cortical control (Fitzgerald, 1993, 1999).

The spinal cord level has three important nociceptive functions: (1) reflexive protective local responses, (2) ascending pain transmission, (3) modulation of nociceptive impulses, and descending pain pathways (Bonica, 1991; Byers, 2001).

Local Spinal Cord Responses. Nociceptive transmissions through Aδ fibers enter the spinal cord by way of the dorsal roots and synapse with neurons in the dorsal horn of the spinal cord known as Rexed's laminae, specifically laminae I and V (Bonica, 1991; Byers, 2001). At the synaptic junction, neurotransmitters such as adenosine triphosphate, glutamate, neurokinin A and substance P are released. Polymodal C fibers synapse with neurons in laminae II and III. These signals spread from the same and adjacent segments of the spinal cord and locally stimulate efferent somatomotor neurons in the anterior horn. The efferent somatomotor stimulation produces skeletal muscle spasm at the site of injury and reflex withdrawal. Vasoconstriction in the skin and splanchnic region is caused by stimulation of preganglionic sympathetic neurons of the autonomic nervous system (lamina VII) in the intermediolateral column located in the synapses of the anterior horn (Byers, 2001).

Within the spinal cord, stimulation of N-methyl-D-aspartate (NMDA) and tachykinin receptors by glutamate and tachykinin, mediate nociceptive transmission. NMDA-dependent C fiber-evoked depolarization of spinal cord cells and central
sensitization or “wind-up” of cells to repeated C fiber stimulation has been demonstrated in young rat pups’ (eight to fourteen days) spinal cords in vitro (Li, Simone, & Larson, 1999; Sivilotti, Gerber, Rawat, & Woolf, 1995). The neonatal spinal cord has a higher concentration of NMDA receptors in the gray matter than that observed in older animals (Gonzales, Fuchs, & Droge, 1993). All laminae in the neonatal dorsal horn are uniformly labeled with NMDA-sensitive glutamate, derived from substance P and glutamate, until ten to twelve days after birth, after which higher densities concentrate in the substantia gelatinosa, (binding is similar to that in adults by day thirty). This excitability spreads to receptors both above and below the spinal level, innervating the area of tissue damage (central sensitization) (Fitzgerald, 1985, 1999, 2000). This increased expression of NMDA receptors in the dorsal horn of the spinal cord accentuates the low pain threshold of preterm and term infants and is thought to be associated with the increased vulnerability of excitotoxic damage in the newborn brain (Kim, Foy, & Thompson, 1996) resulting in stronger and more prolonged pain for the infant (Fitzgerald, 1991b). NMDA receptors are thought to be responsible for the central sensitization or wind-up phenomenon where sensory inputs to the CNS are amplified, resulting in an alteration of the CNS and increased pain (Cui, Meyerson, & Lindeoth, 1999). This wind-up phenomenon, or hyperalgesic state, has been observed in both preterm and term neonates exposed to sequential painful procedures. The increased excitability of nociceptive neurons in the dorsal horn also causes the secondary hyperalgesia that occurs in the normal tissue surrounding the site of injury (Raja, Meyer, & Ringkamp, 1999); thus, more robust pain responses are elicited with less invasive stimuli, suggesting hypersensitivity (Fitzgerald et al., 1989; Gunnar, 1992). In addition, non-nociceptive
input from the opposite limb can cause infant pain. Prolonged activity may be perceived as chronic pain or discomfort and, therefore, may have greater biologic and clinical importance for critically ill infants (Anand, 1993; Macintosh, 1997).

The affinity of the receptor for NMDA decreases with postnatal age. NMDA-evoked calcium influx in rat substantia gelatinosa neurons is very high in the first postnatal week then declines to adult levels by six to eight weeks post-natally (Horii & Kandda, 1994). The amount of current associated with immature NMDA receptors is initially much greater in neonates compared to adults and declines with age and synaptic activity. This is due to a developmental switch in the subunit composition of the NMDA receptor (Flint, Maisch, Weishaupt, Kriegstein, & Monyer, 1997). Glutamergic synaptic currents undergo a characteristic pattern of maturation and development. This pattern involves changes in the kinetic of NMDA receptor currents and the formation of “silent synapses” that initially only express NMDA currents and are only later made functional by the addition of AMPA receptor currents. This allows functional networks to be adaptively modified by experience (Feldman & Knudsen, 1998).

**Ascending Pain Transmission.** Ascending pain pathways are mature in the developing preterm of twenty weeks’ gestation (Anand, 1995; Fitzgerald, 1993). Increase in heart and respiratory rates (autonomic) associated with skin injury, along with the facial pain expression provide evidence of maturity of ascending pathways. These protective autonomic responses and facial responses triggered by the ascending pain fiber connecting with the reticular activating system and the periaqueductal gray (PAG) area are not dependent on cortical input. Brow bulge, eye squeeze, and nasolabial fold have been exhibited in infants as young as twenty-six weeks’ gestation in response to heel
lance procedures (Craig et al., 1992; Johnston, Stevens, Yang, & Horton, 1996). The same expression is associated with pain in adults, although in infants younger than thirty weeks’ gestation, the response is not as robust or universal.

Primary sensory afferent nerve cell bodies are located in the dorsal root ganglion and terminate at the dorsal horn laminae I, II and V. Noxious stimuli transmitted by spinal interneurons are conducted to the brain by the ascending spinothalamic tract. Both A\(\delta\) and C fibers divide on entering Lissauer's tract and send fibers down one segment and up one or two segments of the spinal column (Terman & Bonica, 2001). Substance P and somatostatin, released from the axons of the primary sensory afferents activate dorsal horn interneurons. Neurons in laminae I contain both nociceptive-specific and wide-dynamic-range neurons and contribute to the spinothalamic tract system. Collateral cells or interneurons synapse with cells in other laminae. Conducted by the spinoreticular tract, C fiber impulses terminate in the intralaminar thalamic nuclei, and relay to the limbic cortex. A\(\delta\) impulses pass through the spinothalamic tract to specific relays in the ventral posterolateral thalamic nuclei and on to the somatosensory cortex (Terman & Bonica, 2001). Most of the fibers in the spinothalamic tract are comprised of A\(\delta\) and C fibers which synapse in laminae V and wide-dynamic-range cells synapsing in laminae I.

Transmissions by second-order neurons to the brain stem and thalamic regions occur where noxious stimuli can be further distributed throughout the brain. Sometimes referred to as anterolateral tract or ventrolateral tract, the spinothalamic tract contains several tracts. (1) the neospinothalamic tract, which is primarily sensory discriminative. (2) the paleospinothalamic tract. (3) the spinoreticularthalamic tract, and (4) the spinomesencephalic tract (Byers, 2001).
The neospinothalamic tract is responsible for the autonomic responses to pain, has fewer synapses in the spinal cord, and projects first to the thalamus and then to the primary sensory cortex. Aδ fiber impulses are transmitted on this tract. Aδ fiber impulses rapidly reach the brain providing information about pain location without emotional connotation (Byers, 2001; Coda & Bonica, 2001).

The paleospinothalamic tract is composed of the second-order neurons from laminae I and V. These neurons cross over the spinal column providing collateral fiber connections with the reticular formation of the brain stem, the PAG area, the hypothalamus, and the medial portions of the thalamus. Second-order neurons synapse with third-order neurons in the thalamus allowing the pain stimulus to ascend through these axons to the limbic system and somatosensory cortex (Byers, 2001; Coda & Bonica, 2001). C fiber impulses travel mainly in the paleospinothalamic tract, which makes a greater number of synapses and does not reach the brain as quickly. The paleospinothalamic tract projects to the limbic forebrain and elicits an emotional response to pain (Banasik, 2000; Fields, 1987).

The spinoreticularthalamic tract differs from the spinothalamic tract because its bilateral ascent in the cord reaches both halves of the brain. It terminates in the intralaminar nuclei and the intralaminar nuclei send projections to the limbic and cerebral cortex (Ranney, 1997). The spinoreticularthalamic tract fibers, therefore, are responsible for alerting the organism to danger (fiber termination in the reticular activating system) and attributing emotion to noxious signals (fiber termination in the limbic system).

The medulla, pons, midbrain PAG area, hypothalamus, thalamus and cortex receive signals from the laminae. C fiber impulses are conducted by the spinoreticular
tract and terminate in the intralaminar thalamic nuclei with relays to the limbic cortex, whereas Aδ impulses pass through the spinothalamic tract to specific relays in the ventral posterolateral thalamic nuclei and on to the somatosensory cortex (Byers, 2001).

The medulla and pons function to assess pain in infants. Neurons in the medulla control the autonomic system (respiration, blood pressure and heart rate), the reticular formation (responsible for state of consciousness, attention and sleep), somatic and visceral afferents of cranial nerves V, VII, IX and X, the dorsal motor nucleus of the vagus nerve and the nucleus ambiguous. Autonomic nervous system stimulation from noxious stimuli produces increased sympathetic tone and decreased parasympathetic tone, which result in an increase in heart rate and blood pressure and decreased gastric activity (Coda & Bonica, 2001). Innervation of the muscles in the pharynx and larynx for vocalization result from stimulation of the visceral efferent fibers found in cells of the nucleus ambiguous.

Originating in the pons, the facial nerve (cranial VII) contains the special visceral efferents that innervate the muscles of facial expression. Specifically, the cells in the intermediate group of facial nerve efferents innervate the following facial muscles: (1) the frontalis muscles and the corrugator supercilli, which create brow bulge, (2) the orbicularis oculi, which create eye squeeze, (3) the zygomaticus, which raises mouth comers and elevates the cheeks (nasolabial furrow) along with secondary elevation of the lower eyelid (Parent, 1996; Rinn, 1984). Innervated by these fibers, the aforementioned upper facial muscles represent emotional states that are not under voluntary cortical control (Rinn, 1984).
Descending pathways and modulation. Spinal cord neurons develop in a ventrodorsal pattern: motor neurons develop first, followed by intermediate neurons, deep dorsal horn neurons and, ultimately, the neurons of laminae II. Projection neurons to the supraspinal area develop before the local interneurons (Fitzgerald, 1999). In adults, the inhibition or modulation of nociceptive impulses received from the periphery occurs when, within the substantia gelatinosa, descending pain pathways release inhibitory interneurons and the neurotransmitters.

There are three descending modulatory pain tracts; (1) the lateral corticospinal tract, (2) the reticulospinal tract and (3) the raphe spinal tract (Terman & Bonica, 2001). Descending ipsilaterally to the medulla, the lateral corticospinal tract fibers originate in the cortex, descend and cross to the contralateral side of the medulla, and to lower levels of the spinal cord. Although the majority of corticospinal fibers descend through the dorsolateral funiculus, a smaller set terminates in the first seven laminae after descending laterally into the anterior corticospinal tract. Providing presynaptic inhibition of substance P for receptor sites on the second-order neurons of the ascending pain pathways, fibers from these tracts modulate peripheral afferent nerves in the first 2 laminae through the release of enkephalin or serotonin, norepinephrine, acetylcholine, neurotensin, $\gamma$-amino butyric acid (GABA), glycine and dopamine. Sensory input is thus attenuated before being transmitted to the ascending pathways. Originating in the motor cortex, the corticospinal tract has terminals in laminae VI through IX.

The reticulospinal tract has two branches. The first branch fibers from the nucleus gigantocellularis send fibers to laminae VII and VIII. The second branch fibers originate in the magnocellularis of the rostral medulla, descend laterally to the dorsal horn and
terminate in laminae I, II and V through VIII. Inhibition of wide-dynamic-range and nociceptive-specific cells in laminae I and V result from norepinephrine released from these axons. PAG axons communicate with several regions of the medulla to forward signals through the descending tract (Terman & Bonica, 2001).

The third descending tract, the raphe spinal tract, originates in the nucleus raphe magnus, bifurcates at the upper medulla and sends axons to dorsal regions of the lower medulla and the spinal cord. The fibers in this system produce analgesia at the spinal level through the release of serotonin at their terminals. Although axons from the raphe spinal tract primarily terminate in laminae I, II and V, axons from this system send terminals to all laminae except III, IV and VIII (Terman & Bonica, 2001). In addition, descending fibers from the reticulospinal tract inhibit motor responses. Both neurotransmitters and interneurons must be present in a sufficient amount to modulate pain impulses in the laminae.

Incoming afferent nociceptive signals are modified and can be suppressed at the cord level in the laminae I, II (substantia gelatinosa), IV, V, VI and X through interaction with collateral neurons and descending neurons from the midbrain PAG area, medullary reticular nuclei, paraventricular hypothalamic nucleus, pontine lateral tegmental field, nucleus raphe magnus, and somatosensory cortex (Fields & Basbaum, 1994; Holland, Gammill, & Mackey, 1990; Rinn, 1984). The dorsal horn contains opiate receptors that may have a role in modulating pain. When opioids are administered or when endogenous opioids are released, they bind to the opioid receptors and inhibit the release of neurotransmitters that propagate the pain impulse. Those neurotransmitters are substance
P, somatostatin, calcitonin gene-related peptide, vasoactive intestinal polypeptide and glutamate.

Descending inhibitory controls are immature at birth (Fitzgerald, 1991a). Descending inhibitory pathways progress downward from the brainstem via the dorsolateral funiculus of the spinal cord to the dorsal horn in fetal life. Once noxious transmission and pain perception has occurred, fibers in the spinothalamic tract stimulate regions of the midbrain that send descending projections to the dorsal horn to modulate pain impulses. However, these inhibitory pathways do not extend collateral branches into the dorsal horn for some time and do not become functionally effective until P10 in rats (Fitzgerald & Koltzenburg, 1986). This delay may be due to deferred expression of serotonin and noradrenaline or the immaturity of crucial interneurons. Interneuron maturation in the substantia gelatinosa occurs largely in the postnatal period and appears to be particularly important in the modulation of nociceptive stimuli (Bicknell & Beal, 1984). The lack of descending inhibition in the neonatal dorsal horn means that there is an immature endogenous analgesic system to diminish noxious inputs as they enter the CNS. Thus the effects of the noxious inputs may be more profound in infants compared to adults. This mechanism also explains why the stimulus-produced analgesia from the periaqueductal gray is not effective until P21 in rats (Van Pragg & Frenk, 1991).

Neurotransmitters are essential components of adult and neonatal pain transmission. Adult and neonatal pain transmission is mediated at the level of the spinal cord by the neurotransmitters substance P, somatostatin, calcitonin gene-related peptide, vasoactive intestinal polypeptide, and glutamate. Modulation of pain transmission occurs through the local release of endogenous opioids, enkephalin or serotonin, norepinephrine,
acetylcholine, neurotensin, and γ-amino butyric acid (GABA), glycine, and dopamine from the PAG area. In neonates, however, GABA is transiently overexpressed in the developing spinal cord. During the first two postnatal weeks, the expression of the GABA-synthesizing enzyme, glutamate decarboxylase (GAD), indicates 50% of neurons are GABA-positive compared to 20% GABA-positive neurons in the third postnatal week (Terman & Bonica, 2001).

In the adult spinal cord, GABA is an inhibitory amino acid transmitter that produces membrane hyperpolarization through the activation of postsynaptic GABA_A and GABA_B receptors and depresses transmitter release acting through presynaptic GABA_B receptors. Thus GABA has a crucial role in preventing the spread of excitatory glutamatergic activity. In 90% of embryonic dorsal horn neurons cultured for more than a week, both GABA and glycine induced an increased calcium and cellular depolarization (Reichling, Kyrozis, Wang, & Mcdermott, 1994). This effect decreased with age in culture so that by thirty days it was absent and these agents caused hyperpolarization (Wang, Reichling, Kyrozis, & Mcdermott, 1994). This phenomenon where GABA mediates most of the excitatory drive in the immature brain also occurs in the supraspinal area of the postnatal rat brain (Ben-Ari, Khazipov, Leinekugel, Caillard, & Gaiarsa, November 1, 1997).

In the preterm infant, dopamine and norepinephrine are not available to modulate nociceptive activity before thirty-six to forty weeks’ gestation. Moreover, the inhibitory fibers extending from the PAG area and other areas in the brainstem do not release serotonin until approximately six to eight weeks after birth (Anand, 1995; Fitzgerald, 1999; Marti et al., 1987; Porter et al., 1999). As a result, the infant is limited in the ability
to modulate pain and may experience a greater intensity of pain until forty-eight weeks’ post-conceptual age (PCA). This is consistent with the evidence that some inhibitory mechanisms attributed to interneuronal activity in the dorsal horn are not functional in the newborn (Andrews & Fitzgerald, 1994).

The maturation of C fiber synaptic connections in the dorsal horn, interneuronal development in the substantia gelatinosa, and the functional development of descending inhibitory systems from the supraspinal centers occur post-natally in the rat. That being so, modulatory mechanisms reach maturation later than the basic excitatory mechanism from low-threshold inputs; thus, a newborn infant will mount a clear response to painful stimuli. This response, however, may not always be predictable or well organized. Lack of inhibition contributes to exaggerated and generalized responses to all low and high thresholds of sensory inputs, whereas specific pain responses may require convergent afferent inputs building up over time to become clinically apparent (Fitzgerald, 2000). The onset of the inhibitory processes, therefore, is a crucial determinant of the neuron’s firing activity and ultimately the emergence of pain responses in infants.

Supraspinal Integration of Pain, Perception

This level of pain conduction and modulation occurs in the thalamus, midbrain PAG area, reticular formation, limbic system and cortex. These structures receive and modify pain signals and initiate defensive mechanisms to protect the body from environmental challenges; therefore, their contributions are discussed within the context of integration and modulation of pain responses.

With the exception of olfactory impulses, all sensory impulses are integrated and modified in the gray masses of the thalamus before thalamocortical projections carry the
modified messages to the parietal (somatosensory), temporal (memory) and frontal (associative) lobes. Acting as a subconscious sensory integrator, the thalamus maintains and regulates consciousness, alertness, attention and emotional aspects accompanying sensory experiences. Thalamic lesions may compromise the discriminative aspects of pain such as intensity, locality, and relative position in space/time. Pain, temperature and tactile sensations are integrated at the thalamic level with the limbic system and numerous other sources of sensory input. These marked affective components are communicated behaviorally through the cranial and autonomic nerves (Parent, 1996).

The midbrain PAG area receives afferent stimuli from forebrain limbic areas, as well as sensory and autonomic-related structures in the brain stem and spinal cord; however, the largest number of afferent stimuli come from the hypothalamus (Behbehani, 1995). In the preterm infant, the majority of the ascending input to the PAG area originates principally from lamina I, which receives A\(_\delta\) and C fiber input. The ascending and descending neuronal projections serve as a major integration site for homeostatic control and limbic motor output in the PAG area. The major pain functions of the PAG area are processing and modulation of pain, vocalization and autonomic regulation. Stimulation of the PAG area simultaneously can produce facial expressions of fear, anxiety and pain, anti-nociceptive modulation, and cardiovascular changes in blood pressure and heart rate (Craig & Dostrovsky, 1999). These interconnections with the reticular formation enable the PAG area to integrate the emotional aspects of cardiovascular regulation in responses to pain and fear (Behbehani, 1995).

Displaying nociceptive response characteristics associated with large receptive fields, the reticular formation receives direct input from spinal laminae I and V cells and
projects to the thalamus and back to the spinal cord. Although research has not been able to establish the role these cells play in pain physiology (Craig & Dostrovsky, 1999), the reticular formation is responsible for alerting responses associated with the perception of threat.

Direct projections from the ascending pain pathways are integrated in the hypothalamic centers and limbic system. The limbic system’s reciprocal connectivity with the hypothalamic neurons suggests that each center’s neurons contribute to the emotional responses to painful stimuli. Almost all areas of the CNS that provide autonomic control of visceral organs are connected to the hypothalamus (Craig & Dostrovsky, 1999). Research on limbic system function in infants is insufficient.

The parietal and frontal lobes’ sensory and motor areas are connected to the thalamus, which receives and projects impulses reciprocally. In adults, the cortical level profoundly modifies and controls pain, however, the thalamus processes tissue damage and visceral afferent (sympathetic) pain (Parent, 1996). After synthesizing somatosensory, associative, and temporal (memory) cortical input, the cortex sends signals to the thalamus, influencing pain behavior. Research related to infant cortical pain modification is incomplete. Further research is necessary to determine the role of the thalamus in infant pain perception.

**Embryology of the Central Nervous System**

Early studies of neurologic development in human infants concluded that neonatal responses to pain were decorticate in nature and that perception or localization of pain was not present (Darwin, 1872; Decartes, 1662; Procacci & Maresca, 1994). Sufficient evidence exists to support the infant’s anatomic and functional neurologic capacity for
nociceptive activity before birth (Fitzgerald, 1993, 2000). Fetal neuroanatomy, neurophysiology and neurochemical systems are sufficiently developed to enable preterm neonates to respond to tissue-damaging stimuli.

The spread of cutaneous receptors is preceded by the development of synapses between sensory fibers and interneurons in the dorsal horn of the spinal cord, which first appear during the sixth week of gestation (Anand & Hickey, 1987). Cutaneous sensory receptors appear in the perioral area of the human fetus by seven weeks’ gestation. The receptors spread to the rest of the face, the palms of the hands and soles of the feet by the eleventh week, to the trunk and proximal parts of the arms and legs by the fifteenth week, and to all cutaneous and mucous surfaces by the twentieth week (Anand & Hickey, 1987). At term, the density of nociceptive nerve endings in the skin of the newborn is similar to or greater than in adult skin (Anand & Hickey, 1987).

The lack of myelination has been proposed as an index of maturity for the neonatal nervous system and is frequently used to support the argument that premature or full-term infants are incapable of pain perception (Anand & Hickey, 1987); however, even in the peripheral nerves of adults, nociceptive impulses are carried through unmyelinated (C-polymodal) and thinly myelinated (A-δ) fibers. Incomplete myelination merely slows conduction velocity in the nerves or central nerve tracts of neonates, which is completely offset by the shorter interneuron and intermuscular distances traveled by the impulse. Nociceptive nerve tracts in the spinal cord, moreover, undergo complete myelination during the second and third trimesters of gestation. Pain pathways to the brain stem and thalamus are completely myelinated by thirty weeks’ gestation, whereas the thalamocortical pain fibers in the posterior limb of the internal capsule and corona
radiata are myelinated by thirty-seven weeks’ gestation. The increased density of nociceptive nerve endings and the conductivity of unmyelinated fibers suggest that infants under six-eight weeks of age may be more sensitive to pain than the term or older infant (Stevens & Franck, 1995).

In the developing preterm infant, the fetal cortex of the brain begins at eight weeks’ gestation and by twenty weeks’ gestation, each cortex has a full complement of $10^9$ neurons. Dendritic processes of cortical neurons show arborization, and develop synaptic targets for intracortical connections that are complete by twenty weeks’ gestation. By twenty-four to twenty-six weeks, incoming thalamocortical fibers and synaptic connections are completed (Anand & Hickey, 1987). Somatosensory-evoked potentials are slow and simple before twenty-nine weeks’ gestation; however, by forty weeks, the pattern is complex and latency is short. The cerebral cortex is functionally mature (including the sensorimotor cortex, limbic system, diencephalon, thalamus, midbrain brainstem regions) by twenty-two weeks’ gestation and bilaterally synchronous by twenty-seven weeks (Anand & Hickey, 1987; Prechtl, 1974; Spehlmann, 1981).

Cortical cell migration from the germinal lining of the ventricles in which they originate to specific locations in the cortical plate is complete at approximately twenty-four weeks’ gestation (Als, 1999). The support structure of the germinal matrix is still highly vascular after the completion of cell migration until twenty-eight weeks’ gestation, making the support structure extremely vulnerable to hemorrhage (Volpe, 2000). During the process of migration and differentiation, apoptosis or programmed cell death eliminates a large number of neurons from diverse areas of the cerebral cortex (Anand & Scalzo, 2000). The number of cortical neurons reaches the maximum at twenty-eight
weeks’ gestation and then declines by approximately 70% before birth (Rabinowicz, De Courten-Meyers, & Petetot, 1996).

Infants can mount a stress response with catecholamine production by mid-to-late gestation. Neuropeptides that mediate analgesia are present and functional in early gestation and continue to increase throughout the fetal period. The fetus can produce endorphins in response to asphyxia, acidosis and maternal drug addiction before birth. However, at forty weeks’ gestation, the endorphin system is not functionally mature in terms of analgesia. Additional research has indicated that inhibitory mechanisms mature with increasing gestational age (Anand & Carr, 1989); therefore, the responses of term infants may be less defined than those of older infants (Fitzgerald, 2000). These studies suggest that developmental factors must be considered when proposing pain-relieving interventions for infants.

The anatomical development of the somatosensory cortex, cerebral cortex, thalamus and hypothalamus are present very early in gestation. Similarly, the sensory fiber development and the synapses with interneurons in the dorsal horn of the spinal cord are complete by approximately mid-gestation with functional A-δ and C fibers to transmit pain impulses (Anand & Carr, 1989; Humphrey, 1964). The hypothalamus-pituitary-adrenal-axis that is responsible for maintaining endocrine, autonomic, immunological and behavioral homeostasis is well established by mid-gestation; however, its ability to modulate appropriate pain responses is influenced by gestational age with the most immature neonates experiencing the least protective responses (Plotsky, Bradley, & Anand, 2000).
The excitatory neurotransmitters associated with the transmission of pain (including substance P, glutamate, and calcitonin gene-related peptide) are present in the dorsal horn by approximately eleven weeks’ gestation. The neuropathways for pain perception are present in newborn neonates and the density of nociceptive nerve endings in the skin of neonates is greater than in adult skin. The abundance of NMDA receptors during the first few days after birth suggests that pain transmission is increased in neonates compared to adults or older infants, and, therefore, should be taken into consideration when assessing and managing pain (Anand & Hickey, 1987).

Gestational age and developmental maturity influence pain responses. As early as twenty-seven weeks’ gestation, infants' physiologic and facial responses to heel lance are significantly different from sham heel lance (touch), which indicates clear differentiation of touch from nociception (Johnston et al., 1996). Sensory and functional maturity of the fetal and neonatal cortex have been shown via visual and auditory response patterns on electroencephalograms in infants younger than thirty weeks’ gestation (Torres & Anderson, 1985) and by measurements in vivo of cerebral glucose use in the sensory areas of the brain (Anand & Carr, 1989; Anand & Hickey, 1987; Johnston et al., 1996). In the preterm infant, moreover, neurological connections are in place for the perception of, reaction to, and memory of pain on the cortical level (Dalla Barba et al., 1991).

Pain responses in newborn infants are similar, but significantly less robust compared to older infants (Anand et al., 1999; Andrews & Fitzgerald, 1994; Coskun & Anand, 2000; Craig & Grunau, 1993; Fitzgerald, 1985, 2000; Johnston et al., 1996; Walden et al., 2001), rendering this population at risk for inadequate pain management and contributing to long-term physiologic and behavioral sequelae when exposed to
repeated painful stimuli. In infants less than six to eight weeks, as well, the capacity of the descending inhibitory mechanisms to modulate pain intensity is immature. The research summarizing the neuroanatomy and neurochemistry of nociception in neonates is summarized in Table 2.2.

Infant Pain Management

Assessment of Infant Pain

Infant Pain Responses


Physiologic Responses. The systems modulating pain are integrated with the cardiovascular and respiratory systems (Randich & Maixner, 1984). The most common physiologic responses include those observed with the stress response: (1) increased heart rate, respiratory rate and intracranial pressure, (2) decreases in vagal tone, oxygen saturation and blood pressure, and (3) autonomic changes such as skin color, nausea, vomiting, palmar sweating and dilated pupils (Craig, Whitfield, Grunau, Linton, & Hadjistavropoulos, 1993; Randich & Maixner, 1984; Soetenga et al., 1999; Stevens & Johnston, 1994; Yaster, Krane, Kaplan, Cote, & Lappe, 1977).
<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Neuroanatomy</th>
<th>Neurochemistry</th>
<th>Clinical Applications</th>
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<tbody>
<tr>
<td>6th Week</td>
<td>Cerebral cortex: Development of synapses between sensory fibers and receptive neurons in the dorsal horn</td>
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<td>7th Week</td>
<td>Peripheral nervous system</td>
<td>Appearance of neuropeptides (somatostatin, prostaglandins) in dorsal horn</td>
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<td>8th Week</td>
<td>Cerebral cortex: Fetal cortex begins and by 20 weeks the cortex has a full complement of neurons, 10⁸</td>
<td>Enkephalin, GABA appear in the dorsal horn</td>
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<td>12-14th Week</td>
<td>Spinal Cord Cell differentiation begins in dorsal horn</td>
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<td>16th Week</td>
<td>Cerebral cortex: Dendritic process or cortical neurons proliferate and develop synaptic targets for incoming thalamocortical fibers and intracortical connections</td>
<td>Substance P appears in the dorsal horn</td>
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<tr>
<td>20th Week</td>
<td>Cerebral cortex: Cortical hemispheres have full compliment of neurons</td>
<td>B endomorphins observed in anterior and intermediate lobes of the pituitary gland</td>
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<td>22nd Week</td>
<td>Cerebral cortex: Dendrites begin to develop and migrate towards synaptic targets. Functional maturity of cortex is demonstrated by fetal and neonatal EEG patterns that are evident by 22</td>
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<td>Weeks Gestation</td>
<td>Description</td>
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<td>20 – 24&lt;sup&gt;th&lt;/sup&gt; Week</td>
<td>Cerebral cortex: Thalamocortical connections established and continue to synapse until 5 years postnatal life.</td>
<td>Hypersensitivity to pain and touch near injured areas (hyperalgesia, allodynia, central sensitization) global motor responses to pain, slow or absent facial responses; non tactile stimuli such as handling, diaper changes, or bathing may be perceived as painful; vulnerable if IVH related to increase in blood pressure associated with pain until 28 weeks.</td>
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<tr>
<td>24 – 26&lt;sup&gt;th&lt;/sup&gt; Week</td>
<td>Peripheral nervous system: mature; cutaneous receptors have lower pain threshold, threshold decreases further after noxious stimuli. Spinal Cord: Mature ascending pathways; immature descending pathway; receptive field of dorsal horn cells are large and begin to diminish 2 weeks postnatally. Cerebral cortex: functionally mature; somatosensory evoked potentials are slow and simple; germinal matrix is highly vascular after migration is complete at 24 weeks.</td>
<td>Continued hypersensitivity; facial responses to pain robust and discriminatory; motor responses become more localized with repeated stimuli; infants may anticipate noxious events.</td>
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<tr>
<td>27 – 29 Weeks</td>
<td>Peripheral nervous system mature. Spinal Cord: Mature cutaneous limb withdrawal reflex; immature descending pathways. Cerebral cortex: Maximum number of cortical neurons is reached; cerebral cortex is bilaterally synchronous; somatosensory potentials are slow and simple.</td>
<td>Continued hypersensitivity.</td>
<td></td>
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<tr>
<td>37 - 40th Week</td>
<td>Pathway, nociceptive pathways to the brainstem and thalamus are myelinated, well defined periods of sleep and wakefulness. Cerebral cortex: Mature visual and auditory cortical responses.</td>
<td>Continued hypersensitivity</td>
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<tr>
<td>Peripheral nervous system mature</td>
<td>Spinal Cord: Increased dopamine and norepinephrine in descending pathway. Cerebral cortex: cortical neurons reduced to 70% through apoptosis; somatosensory potentials are short and complex; thalamocortical connect are myelinated.</td>
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<tr>
<td>42 Weeks</td>
<td>Spinal Cord receptive field of dorsal horn cells begin to diminish.</td>
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<td>6-8 Months post-natal</td>
<td>Peripheral nervous system mature</td>
<td>Capable of modulating pain</td>
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<td>Spinal Cord: Mature descending pathway as serotonin is available. Cerebral cortex: apoptosis complete; number of cortical cell stable.</td>
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Abbreviations: IVH, Intraventricular hemorrhage

Note. Data from Anand, 1993; Anand & Carr, 1989; Fitzgerald, 1993; Fitzgerald, 2000; Fitzgerald & Anand, 1993; Humphrey, 1964,
The hypothalamic-pituitary-adrenal (HPA) axis represents a regulatory system that modulates different types of stressors to maintain equilibrium within the endocrine, autonomic, immunological and behavioral systems (Plotsky et al., 2000). The HPA axis conveys impulses such as pain, touch or pressure to neurons in the hypothalamus. These neurons produce peptides that travel to the anterior pituitary gland where corticotrophin-releasing factor (CRF) and arginine vasopressin (AVP) encourage the release of stored adrenocorticotropic hormone (ACTH) into the system circulation. ACTH stimulates the synthesis and secretion of glucocorticoids from the adrenal cortex to mobilize energy substrates during stress in synergy with catecholamines released from the adrenal medulla. The resultant effect is stress-induced hyperglycemia, mobilization of fat and protein, insulin resistance, and increased heart rate and blood pressure. Although these HPA effects may be productive at times, their prolonged effects have detrimental consequences (Anand et al., 1985).

The HPA responds with decreased sensitivity in newborn infants. The hypothalamic and pituitary components of the HPA are established early in fetal life; however, the establishment of the adrenal cortex is delayed. This results in the infant's ability to respond to pain, but the HPA is not mature enough to mobilize glucocorticoids to maintain endocrine, immunological and behavioral stability. Infant exposure to repeated painful procedures facilitates the absence of the negative feedback of CRF and ACTH, thus magnifying the catabolic state and contributing to long-term neurological sequelae (Plotsky et al., 2000).

Term infants who received anesthesia intra-operatively had decreased physiologic instability (increased heart rate, blood pressure, and intracranial pressure) and improved
clinical outcomes including decreased incidence of sepsis, metabolic acidosis, hyperglycemia and disseminated intravascular clotting (Anand et al., 1985; Anand & Carr, 1989; Anand & Hickey, 1987). Analgesia administered to preterm infants undergoing thoracotomies (Anand & Hickey, 1992) or mechanical ventilation (Kelly & Finer, 1984; Raju, Vidyasagar, Torres, Gruñid, & Bennett, 1980) experienced reduced heart rate and blood pressure during the procedure. Preterm infants who did not receive analgesia for these noxious stimuli had adverse physiologic responses and were more at risk for developing intracranial hemorrhage, pneumothorax or other complications than the infants who received analgesia (Anand & Hickey, 1992).

Hormonal and metabolic responses have been measured in fetuses (Giannakoulopoulos, Sepulveda, Kourtis, Glover, & Fisk, 1994), in preterm (Anand et al., 1985; Stevens & Johnston, 1994) and term (Anand, 1995; Clancy et al., 1992; Kehlet, Brandt, & Rem, 1980; Porter, Wolf, Gold, Lotsoff, & Miller, 1997) infants undergoing minor procedures and surgical operations. Hormonal and metabolic responses during painful procedures in term infants stimulate the release of catecholamines, corticosteroids, growth hormones, glucagons, epinephrine and norepinephrine that increase heart rate, blood pressure, enhance liver and muscle glycogen breakdown, stimulate metabolic rate, and improve mental activity (Anand & Hickey, 1987; Clancy et al., 1992; Guinsburg et al., 1998). In term infants undergoing cardiac surgery, anesthesia blunted stress responses and facilitated wound healing (Anand & Hickey, 1987).

Behavioral Responses. Theoretical explanations of pain responses using the neonatal facial coding system (Grunau & Craig, 1987), behavior state organization, (Prechtl, 1974), and neurodevelopmental status and gestational age (Als, 1999) is
required to examine pain responses for healthy and acutely ill young infants. Infants are highly organized involuntary systems. In newborns, the facial nerve arranges facial features in configurations specialized for communication (Grunau & Craig, 1987). The infant’s face has the capacity to display a remarkable diversity of patterns within a brief span of time. This diversity of patterns reflects the infant’s varied subjective states and provides specific information regarding pain. The inherent biologic value of non-verbal facial communication is reflected in the infant’s ability to seek out and perceive human faces at a very early age. By three months of age, infants’ demonstrate preferential gazing patterns for facial over non-facial stimuli (Craig, Korol, & Pillai, 2002).

Infant behavioral response to tissue insult include cry, avoidance, gross motor activity, and facial expression. The unique configuration of facial activity at birth for term infants is a temporally integrated, relatively stereotypic pattern in infants reacting to invasive procedures (Grunau & Craig, 1987; Grunau, Johnston, & Craig, 1990; Stevens & Johnston, 1994). The duration of facial expression is sensitive to changes in pain intensity and thus has utility for evaluating pain-relieving interventions (Grunau et al., 1990; Stevens, Johnston, Petryshen, & Taddio, 1996). Volitional facial movements involve mainly cortical activity, whereas involuntary movement involves mainly subcortical systems (Grunau & Craig, 1987).

Adults systematically use facial activity when judging pain in infants. The facial expression of pain in neonates resembles the facial activity in adults experiencing pain and has been shown to vary with the neurobehavioral state of the infant at the time of injury (Grunau & Craig, 1987). The neonatal facial expression of pain (Yaster et al., 1977), shown in the model in Figure 2.1, is characterized by furrowed brow, eye squeeze,
deepening of the nasolabial furrow, vertical and horizontal stretched lips and cupped tongue. The cupped tongue is present only during infancy and represents a vigorous response to pain. The most sensitive indicators of pain in full-term infants during heel lance are eye squeeze, brow lowering and deepening of nasolabial furrow. The most sensitive indicators irrespective of gestational age or maturation were the presence of taut tongue and vertical stretched mouth (Craig et al., 2002). Stevens et al. (1996) found brow bulge, eye squeeze and nasolabial furrow were consistent facial expressions following painful stimulation.

Using the heel lance procedure, body movements were examined as an indicator for pain (Craig et al., 1993; Franck, 1986; Walden et al., 2001). Consistent with facial activity, the maturity of the neurologic system and the infant’s age affected the quality of the infant’s movement; however, in contrast with the findings using facial activity, infants displayed a significant response to the alcohol swab and an even greater response to the heel lance confirming the capacity of infants to differentiate one invasive procedure from another. Acutely ill infants may lack sufficient energy to demonstrate body movements in response to noxious stimuli (Craig et al., 1993). Compared to healthy older infants, newborn or acutely ill infants’ movements are less organized and more difficult to identify (Craig et al., 1993; Holsti, Grunau, & Whitfield, 2002; Johnston et al., 1996).

In contrast to gross motor movements, flexor withdrawal reflex is a measure of nociceptive function in the CNS that parallels perceived pain in adults (Gibbins et al., 2002). There is a significant distinction between the flexor withdrawal reflex and the
Figure 2: Neonatal facial coding system. With considerable consistency, newborns react to tissue insult with brow lowering, eyes squeezed shut, deepening of naso-labial furrow, open lips and mouth, and a taut, cupped tongue.

Babinski reflex. The presence of tendon reflexes requires an intact spinal reflex arc. Spinal reflex arcs are fully developed by the eighth week of gestation. Afferent and efferent components are formed earlier than the connecting neurons. The Babinski response, which involves the extension of the great toe with spreading of the remainder of the toes in response to non-noxious stimulation of the lateral aspect of the sole of the foot, is an indication of abnormal cortical function. Its frequent presence in the newborn reflects poor cortical control of motor function by the immature brain (Polin & Fox, 1998).

The withdrawal reflex is a response to noxious stimuli (often accompanied by triple flexion of the hip, knee and ankle) and the contact avoidance response associated with holding the dorsum of the foot which tends to cause an extensor response of the toes. These factors indicate that the observed response of the toes is influenced largely by the technique used. Minimal stimulation, such as dragging the thumbnail along the lateral aspect of the sole, results in flexion of the toes in greater than 90% of term newborns. In contrast, a more painful stimulus results in an extensor response in 95% of term infants. Because of these inconsistencies, the plantar response is considered to be of limited value in the examination of pain in the newborn (Polin & Fox, 1998).

Cry can provide information about the neonate’s biological integrity (Lester, 1987; Zeskind & Lester, 1978, 1981) and has been utilized as an indicator of pain (Michelsson, 1971; Michelsson, Jarvenpaa, & Rinne, 1983; Michelsson, Sirvio, & Wasz-Hockert, 1977a; Porter, Miller, & Marshall, 1986; Porter, Porges, & Marshall, 1988). Cry characteristics have been examined by their presence or absence (Owens & Todt, 1984), latency (Franck, 1986), percentage of occurrence and duration (Franck, 1986) and
acoustic parameters (Fuller, 1991; Fuller & Conner, 1995; Stevens, Johnston, & Horton, 1994). Acoustic analysis of cry (fundamentally, the frequency of the first cry following pain) is conceptualized as indicative of the central nervous system’s capacity for response modulation. The pain cry is high-pitched, tense, harsh, non-melodious, short, sharp and loud. The difficulty with utilizing cry as an assessment of pain is the infant's ability to produce a robust cry for reasons other than exposure to a noxious stimulus, or his inability to cry due to the severity of his illness. If the infant is intubated, the infant will be unable to produce a cry due to the presence of an endotracheal tube through the glottis. The presence or absence of cry, therefore, is not a reliable indicator for infant pain.

In an examination of behavior responses of preterm and term neonates experiencing painful and non-painful procedures, Craig et al. (1993) assessed the infant’s behavioral response during the four phases of the heel lance procedure, baseline, swabbing, lance and recovery. Physiologic data, facial and body activity were collected. The response to pain was significant during the heel-lancing phase at all gestational ages. Neonates as young as twenty-five weeks’ gestation demonstrated facial activity in response to heel lancing, although there was less facial activity compared to older neonates. Physiologic response varied with the phases of the heel lance procedure but did not vary with gestation age.

Several studies have examined the correlation of gestational age and pain responses. Johnston, Stevens, Craig, and Grunau (1993) compared the behavioral pain responses of four groups (preterm, term, two and four months of age) of infants during a painful procedure. The findings indicated an increase in the pattern of facial activity during the painful procedure across all gestational ages; however, there was less facial
activity in the preterm group than in the term and older infants’ group. Stevens, Johnston, and Horton (1993) examined preterm infants’ (n=124) physiologic and behavioral responses to heel lances. Brow bulge, eye squeeze and nasolabial furrow were increased during the heel lance and squeeze phases of the heel lance procedure but gestational age was not a significant factor for facial activity. Further research may be indicated due to the narrow range of the gestational age group that was examined (thirty-two to thirty-four weeks’ gestation).

Factors Influencing Pain Responses

Behavioral state organization. A powerful, physiologically-based contextual variable for newborns is their sleep/wake state. The awareness of relatively stable behavioral states and their possible effect on the responsiveness of the infant has evolved from naturalistic observations, either carried out in Prechtl’s studies within the context of human ethnology or Wolff’s observations that behavioral conditions had implications for Piaget’s theory of intelligence and the psychoanalytic theory of development (Prechtl, 1974).

The construct of sleep/wake state offers an important organizational network for studying perceptual systems in infants. State organization is viewed as an indication of the infant’s neurobehavioral status, reflecting the infant’s ongoing internal organization and capacity for integrating environmental input (Grunau & Craig, 1987). Regulation of state cycles is a fundamental function of the nervous system and has its roots in early developmental stages (Prechtl, 1974).

Brain mechanisms are specific to descriptive behavior states. The functional properties of nervous activity are different in the various behavior states. States must be
considered not only as a descriptive behavior classification, but also as distinct modes of brain activity, each having its specific properties and reflecting a particular mode of nervous function. The responsiveness of infants to a variety of stimulus modalities in each state changes the mode of nervous activity and leads to changes in the input-output relation. The differences in responses to various stimuli are dependent on state specificity (Prechtl, 1974).

Pain can influence and be influenced by the infant’s behavioral state. Grunau and Craig (1987) demonstrated that infants present a cohesive response pattern to invasive stimulation, which was consistent with the response capabilities recognized in the other sensory modalities. The reaction pattern, however, is not exclusively the imperative response to tissue insult. Grunau and Craig established that pain expression in infants was a function of ongoing behavioral state rather than a sole reflection of tissue damage. Due to the limited capacity for infants to learn secondary responses to nociceptive input (although intrauterine learning cannot be excluded), Grunau and Craig determined that the differences in facial expression and latency to facial movement and cry across states reflects the capacity of states to modulate pain perception. Stevens et al. (1993) found infants in a quiet sleep state prior to heel lancing had significantly increased cry latency and decreased facial actions compared to infants in active sleep. Infants in active awake states had the highest occurrences of all facial actions.

Co-morbid factors such as severity of illness (Johnston et al., 1996; Michelsson, 1971; Michelsson et al., 1983; Stevens et al., 1993), postnatal age (Grunau, Whitfield, & Petrie, 1994a; Johnston et al., 1993), frequency of prior painful procedures (Johnston et al., 1993; Johnston et al., 1996; Stevens, Johnston, Franck et al., 1999), time interval
between last painful procedure, (Franck, 1986; Johnston et al., 1996) and invasiveness of the painful procedure (Porter et al., 1999) have been associated with altering the infant's physiologic and behavioral responses to pain.

**Neurodevelopmental status and gestational age.** Each infant has a unique response to environment (Als, 1991). Because infants communicate functional stability and stress through their behavior, Als developed a model of infant behavior that characterizes the behavioral organization of the preterm and term infants. According to Als, in the synactive theory of development shown in Figure 2.2, preterm infants are in continual interaction with their environment via five subsystems: autonomic, motor, state, attention/interaction and self-regulation. The autonomic subsystem is distinguished by the pattern of respiration (apnea, tachycardia), color changes (ruddy, pale, dusky, mottled, webbed), and visceral signs (emesis, seizures, twitching). The motor subsystem is manifested in the infant’s posture (hyperflexed, flaccid, extended), specific movement patterns of extremities, trunk, head, face and level of activity. Initially, the state subsystem may be poorly defined, but can be observed in the range of states (sleep, arousal, awake, alert, crying). The attention subsystem is seen in the infant’s ability to orient and focus on sensory stimulation in the environment (faces, sounds, objects). The self-regulating subsystem can be observed in the behaviors that the infant uses to maintain the integrity and balance of the other systems. Because each subsystem functions in relation to other subsystems, the loss or increase of integrity of one subsystem can influence the organization of the others in response to environmental demands.

The ability and quality of an infant’s behavioral response is dependent on the
Figure 2.2 Model of Synactive organization and Behavioral Development

infants’ increasing gestational age. An uncompromised full-term infant achieves stability of the subsystems within days following birth. Excessive stimulation on immature motor state and attention systems places an extreme burden on the central nervous system resulting in physiologic compromise. During physiologic instability, infants exposed to overstimulation may be unresponsive and in an inactive sleep state to conserve energy and maintain homeostasis. An infant is unavailable for stimulation and is stressed when exposed to noxious stimuli (Vandenberg, 1995). In newborn infants, responses to noxious stimuli early in life are expressed physiologically. In contrast, older infant's responses to stimulation are expressed interactionally (Als, 1991). Clues in the infant’s physiological pattern are cues to the appropriateness of stimulation (Vandenberg, 1995).

Infants who are acutely ill or who are exhausted from the number or frequency of painful procedures typically demonstrate a less robust response to pain compared to mature, healthy infants. These infants are often unable to produce a robust cry or may lack sufficient energy to demonstrate body movements in response to pain. Some infants will not demonstrate a change that can be measured within the context of the current understanding of pain indicators. It is to hypothesize that these infants may not have the energy, maturity, or other resources to respond (Stevens, 2001).

Environmental factors such as light, noise, and frequency of handling have been proposed to reduce stress responses by reducing the cumulative stimuli the neonate experiences (Als et al., 1986; Als et al., 1994; Buehler, Als, Duffy, Mcanulty, & Liederman, 1995; Fleisher et al., 1995). The results of environmental factors influencing neonatal pain response warrants further investigation, given that these studies were conducted with small sample sizes and outcomes were not blinded.
Studies have indicated that physiologic and behavioral pain responses differ according to gender. Sternberg, Smith and Scorr (2004) examined gender and age-related difference in mice. Their findings reveal female mice had longer tail-withdrawal latencies and male mice demonstrated a stronger analgesic response to morphine. Moreover, basal pain behavior and analgesic responsiveness was greater in day-old mice compared to week-old mice. Frot, Feine, and Bushnell (2004) found that females rated pain intensity and unpleasantness higher than males did during painful procedures; however, despite the lower pain ratings, males reported more pain-related anxiety than women. Guinsburg et al. (2000) and Zeichner et al. (2000) found physiologic and behavioral pain responses were more robust in female infants, while Grunau and Craig (1987) suggest male infants showed increased responses. Studies by Christy et al. (1995) and Stevens et al. (1994) found no differing responses to pain based on gender. Inconsistencies in the findings indicate a need for future research to examine the influence of these factors on infant pain response.

Behavioral and Environmental Interventions

Non-nutritive Sucking

One of the earliest coordinated behaviors of the fetus is sucking. While necessary for biological survival, sucking is also an important parameter of caregiver-infant interaction, self-gratification and soothing. Newborn infants exhibit two distinct sucking patterns, nutritive and non-nutritive (NNS). In contrast to the long, continuous, rhythmic pattern characteristic of nutritive sucking, non-nutritive sucking has a pattern of shorter, alternating bursts of sucking and rest (Blackburn & Vanderberg, 1998).
Non-nutritive sucking is present in the fetus as early as 4½ months (Blackburn & Vanderberg, 1998). Although very preterm infants display non-nutritive sucking, its presence does not mean the infant has the ability to coordinate and maintain nutritive sucking. The ability to maintain, regulate and organize the pattern and rhythm of nutritive sucking is affected by the infant’s maturity, illness, and experience with sucking.

Infants display non-nutritive sucking when a nipple is placed in the mouth without the presentation of food. Non-nutritive sucking and rhythmic mouthing (seen in quiet sleep) have similar temporal organization with regularity of the sucking-pause pattern. Non-nutritive sucking is a state modulation and organizing activity. It is used during gavage and inter-feeding intervals. It has been associated with decreased activity and crying, decreased intracranial pressure, improved oxygenation, increased quiet sleep, increased alertness for nipple feedings, better weight gain and shorter hospital stays. Non-nutritive sucking can be used to provide the infant with a source of self-consolation and self-regulation (Blackburn & Vanderberg, 1998). Carbajal, Chauvet, Couderc, and Oliver-Martin (1999) propose that NNS provides a superior analgesic effect compared to sweet solutions.

Mechanism of action. The calming effects of NNS have been observed in human and rat neonates; however, the mechanism underlying the effectiveness is unclear. It is hypothesized that NNS produces analgesia in human neonates through stimulation of orotactile and mechano-receptors when a pacifier or non-lactating nipple is introduced in the infant’s mouth (Campos, 1994). Unlike the mechanism of sucrose, the orotactile-induced analgesia associated with NNS does not appear to be mediated through opioid
pathways. It is not affected by the administration of naltrexone and its efficacy is terminated once sucking has ceased (Blass & Watt, 1999).

An alternate hypothesis proposes that serotonin production may be responsible for the calming and analgesic properties associated with NNS (Spear, Frambes, Goodwin, & Moody, 1994; Wang, Bowersox, Pettus, & Gao, 1999; Williams, Rosenblatt, & Hall, 1979; Zagen, Nakash, & Yadid, 1999). The involvement of serotonergic systems in the modulation of pain is well documented in the management of adult pain. In adults, serotonin and serotonin re-uptake inhibitors appear to facilitate the release of $\beta$ endorphins that inhibit the transmission of nociceptive impulses. Blass and Watt (1999) found the calming effects of non-nutritive sucking (greater than 30 sucks/minute) is consistent with the activation of serotonin in infants. The calming effects are stimulus dependent and terminate with the cessation of NNS; thus, the ability to relieve pain appears to be related to the organism’s neuronal ability to produce serotonin.

Sucrose

The administration of sucrose has been the most frequently studied behavioral/environmental intervention for the relief of procedural pain in infants. Sucrose has promoted calming behaviors and reduced acute procedural pain in preterm and term infants (Blass & Hoffmeyer, 1991; Stevens, 1997). Generations of parents and grandparents have anecdotally described the calming and soothing properties of sucrose, claiming that the sweet solutions calm distressed infants. Pharmacists employ sucrose in oral suspensions to conceal the bitter taste of the active pharmacologic ingredient.

Sucrose has the capacity to reduce crying time and distress vocalization by eliciting licking, swallowing and hand-mouth behaviors that prevent crying. Infants who
receive small amounts of sucrose remain in awake and alert states and place their hands in their mouths. Hand-mouth behaviors appear after crying stops, disputing the argument that crying only stops because it incompatible with hand-mouth or sucking behaviors. These results imply that the efficacy of sucrose as a pain-relieving intervention is more complex than simply preventing the licking, swallowing and mouth behaviors that preclude crying (Blass, Fillion, Rochat, Hoffmeyer, & Metzger, 1989).

Mechanisms of Action. Research has established sucrose as an effective analgesic for heel lance (Stevens et al., 2001b). Although several different hypotheses regarding the underlying mechanisms of sucrose exist, the proposal most supported is that the sweet taste of sucrose promotes the activation of endogenous opioids which attenuate nociceptive information at the level of the dorsal horn. The mechanisms underlying the efficacy of sucrose are advanced through indirect evidence for endogenous opioid mediation that has been primarily derived through studies with animal models (Anseloni et al., 2002; Blass et al., 1987; Fidler, Kalman, Ziemer, & Green, 1993).

Ethical reasons mandate that studies exploring the mechanism of action of sucrose use animal models and extrapolate the findings to human neonates. Infant rat pups have been used to study pain development because their pain pathways, mechanisms and neurological maturity are very similar to those of the human preterm neonate at twenty-three to twenty-four weeks’ gestation (Fitzgerald, Shaw et al., 1988). Studies utilizing rat pups have examined sweet taste as the mechanism of action for efficacy of sucrose. Blass et al. (1987) found elevated pain thresholds a few minutes post-administration in ten-day rat pups infused with a 7.5% intraoral sucrose solution. Peripheral sweet stimulation was necessary to maintain the central changes. Blass and Fitzgerald (1988) reported rat pups
preferentially ingest sucrose over milk and other non-sweet solutions during painful and stressful events. Anseloni et al. (2002) compared the analgesic effects of 7.5% sucrose with 0.1M NH₄Cl to eliminate the possibility that the analgesia produced by sucrose was not due to sweetness but to a non-specific activation of taste receptors. Their findings established an 80% increase in paw withdrawal latency after 7.5% sucrose solution that persisted two to three minutes after termination of stimulus (p < 0.01). Infusion of 0.1M NH₄Cl did not alter paw latencies (p > 0.05). Spinal cord Fos protein expression, a measure of neuronal activity, decreased after intraoral sucrose administration. Blass and Hoffmeyer (1991) demonstrated that sucrose is not detected in the mouth until twenty to forty seconds after its delivery and that only a trace amount of sucrose can be detected chemically in the saliva.

Studies investigating the analgesic properties of sucrose propose that there is a biphasic mechanism to the analgesic effect of sucrose. Initially, within ten seconds, a pre-absorptive calming effect seems to be related to the taste of sucrose (Ramenghi, Evans, & Levene, 1999). The second mechanism is the release of endorphins.

The efficacy of sweet tastes appears to provide opioid-mediated analgesia in the rat model; however, repeated doses of sweet tastes results in tolerance to subsequent opioid administration and altered subsequent responses to thermal pain. Rats receiving intraoral saccharine for twenty-eight consecutive days did not respond to morphine for painful thermal stimuli. Unlike the control rats that did not receive saccharine, the experimental rats appeared to develop a tolerance to morphine. The rats that received saccharine did not respond to the opioid antagonist naltrexone (Lieblich, Cohen, Ganchrow, Blass, & Bergmann, 1983). The high levels of endogenous opioids explained
the altered responses associated with exposure to sweet tastes. Although the efficacy of sucrose is reduced in animal models in the presence of high levels of endogenous opioids, the relationship between human neonates and sucrose is theoretical.

The results of animal studies suggest that endogenous opioids in the taste and neurological pathways participate in pain reduction. Research findings conclude that intraoral ingestion of sucrose reduces procedural pain and the effects of parentally administered opioids, implying a common pathway for pain reduction (Fidler et al., 1993). These studies further suggest, following noxious stimuli, the magnitude of analgesia observed with 0.22M sucrose solutions is equivalent to parenteral morphine 0.0625 mg/kg, a marginally sub-therapeutic dose (Blass & Shide, 1994). The analgesic effects of sucrose, moreover, are reversed with concurrent administration of naloxone (Blass & Fitzgerald, 1988; Blass & Shide, 1994; Kehoe & Blass, 1986; Panksepp, Nelson, & Siviy, 1994) Pre-clinical trials suggest sucrose is (1) antinociceptive, (2) effective with short latency and (3) effective after the painful stimulus has ceased.

Similarities in antinociceptive activity between oral sucrose and morphine injections have been demonstrated in newborn rats (Blass & Fitzgerald, 1988; Blass & Shide, 1994; Kehoe & Blass, 1986; Sivilotti et al., 1995) and chicks (Panksepp et al., 1994). Kehoe and Blass (1986) established the reversal of sucrose analgesia with the administration of a non-specific opioid receptor antagonist, naloxone. Rat pups displayed diminished distress vocalizations following an electrical stimulation to their hind paw after the administration of intraoral sucrose. Water did not effect distress vocalizations. Similar reductions in vocalization were reproduced by exogenous morphine
administration and were reversed in the sucrose study with the administration of naltrexone, an opioid antagonist, suggesting opioid mediation.

Naloxone also blocked the analgesic effect of sucrose, demonstrating endorphin release. Blass et al. (1987) and Anseloni et al. (2002) reduced paw lift latencies with the administration of naloxone thirty minutes prior to sucrose administration. The opioid receptor antagonistic effects of naloxone were not affected by the varying concentration of sucrose (11.5% & 7.5%) (Anseloni et al., 2002; Blass et al., 1987).

Evidence for the efficacy of sucrose in humans. Gustatory analgesia in animals and humans is rapid, enduring, and dependent on the ability to detect sweet tastes. As a general rule, taste is a holistic assessment of the interaction of the fundamental taste systems of sweet, sour, bitter, salty and umami ("savouriness"). One of the most widespread myths about taste relates to the distribution of the four basic tastes: sweet, sour, bitter and salty. The tongue map is Boring’s (1942) mistranslation of a German PhD’s thesis published in Philosophische Studien (Hanig, 1901). Boring calculated taste sensitivities by taking the reciprocals of the mean thresholds given in Hänig’s tables. Collings (1974) re-examined the threshold variations and found insignificant variations in taste threshold around the perimeter of the tongue. Collings’ findings suggest the separate populations of taste buds that sense each of the basic tastes are distributed across the tongue.

Taste receptors are present in human neonates by the end of the eighth week of gestation, and sensory nerve fibers from the receptors of the tongue to the brainstem are present by twenty-six to twenty-eight weeks’ gestation. Taste fibers unite in the medulla
oblongata, where they synapse with fibers for touch, temperature and pain and are
relayed to the cerebral cortex for interpretation (Moore & Persaud, 1993).

In preterm, term and older neonates, sucrose has been administered by syringes
(Abad, Diaz, Domenech, Robayana, & Rico, 1996; Johnston et al., 1999; Johnston,
Stremler, Stevens, & Horton, 1997; Ramenghi, Wood, Griffith, & Levene, 1996),
droppers (Rushforth & Levene, 1993), cups (Blass & Shah, 1995; Ramenghi et al., 1999),
or dipped on pacifiers (Graillon, Barr, Young, Wright, & Hendricks, 1997; Ramenghi et
al., 1999; Stevens, Johnston, Franck et al., 1999). These studies advocate administering
sucrose directly on the taste receptors that detect sweetness, believed to be located on the
anterior portion of the tongue.

By twenty-six weeks’ gestation, the intestinal epithelium of a preterm infant is
mature enough to hydrolyze sucrose into glucose and fructose (Aldoretta & Hay, 1995;
Neu & Koldovsky, 1996; Schanler, 1995). Although the duration of analgesic effect of
intraoral sucrose may last as long as seven minutes, the peak effect appears to be two
minutes. Recent studies have used the two-minute interval prior to the painful event as
the time of administration of a single dose (Johnston, Collinge, Henderson, & Anand,
1997; Smith, Fillion, & Blass, 1990). Given the rapid effects of sucrose, taste appears to
mediate the opioid response in humans. It is unlikely that hydrolysis of sucrose in the
small intestine is responsible for its analgesic properties (Aldoretta & Hay, 1995; Neu &
Koldovsky, 1996).

Ramenghi et al. (1999) compared the efficacy of sucrose using different routes of
sucrose administration in preterm neonates. In a crossover design, neonates received
sterile water or sucrose prior to a heel lance. The solutions were gastric loaded through a
nasogastric tube. In the second intervention, the solutions were administered to the neonates via a syringe on the tongue. A behavior pain score (0-15) comprised of facial expression (brow bulge, eye squeeze, nasolabial furrow and open mouth) measured the pain response. Compared to sterile water, sucrose administered directly on the tongue reduced crying time (6 vs. 22 seconds, p = 0.006) and behavioral pain scores (5 vs. 9, p = 0.002). Procedural pain was not reduced when sucrose or sterile water was administered directly into the stomach.

A variety of sucrose concentrations (7.5%, 12%, 24% or 50%), volumes and administration schedules have been implemented to reduce procedural pain in neonates. Various time delays between sucrose intake and the initiation of painful procedures have been used (Blass & Shah, 1995; Stevens, Johnston, Taddio et al., 1999; Stevens & Ohlsson, 1998). Blass and Ciaramitero (1994) found that sucrose calmed neonates as early as nine hours after birth, and the infants remained calm for five to ten minutes after a painful stimulus. The peak effect of sucrose is defined as the amount of time required for taste receptors in the mouth to mediate opioid responses and inhibit nociceptive impulses. The peak effect of sucrose (reduction in crying time) occurs two minutes after administration to the anterior portion of the tongue. When duration of cry is used as an indicator of pain in term infants, 0.24g (2ml of 12% weight/volume sucrose) is efficacious for heel lances (Bucher et al., 1995; Johnston et al., 1999; Johnston, Stremler et al., 1997) and venipunctures (Abad et al., 1996). In preterm neonates, 0.24g (2ml of 12% weight/volume sucrose) is efficacious for heel lances (Blass, 1997; Rushforth & Levene, 1993) and intramuscular injections (Allen, White, & Walburn, 1996; Barr et al., 1995; Lewindon et al., 1998; Ramenghi et al., 2002; Reis, Roth, Syphan, Tarbell, &
Holubkov, 2003). Despite the evidence supporting a reduction in crying time with greater concentrations of sucrose (Haouari, Wood, Griffith, & Levene, 1995) doses greater than 0.5g have not been beneficial for additional pain relief (Stevens et al., 1997; Stevens & Ohlsson, 1998; Stevens et al., 2001b; Stevens, Yamada et al., 2004).

The behavioral and environmental approaches of sucrose and NNS have been studied for procedural pain management in the preterm and term neonate. Stevens et al. (1997) suggest that 2 ml of 12 - 24% sucrose, in the range of 0.24g or 0.50g is effective in reducing pain responses. Whether the sucrose alone or a synergistic effect of sucrose with NNS is responsible for the reduction in pain responses is not clear. It should be noted that most of the studies examined the effects of sucrose on healthy term neonates. Preterm or acutely ill neonates may not tolerate 2 ml of a solution without side effects such as aspiration, bradycardia, tachycardia or desaturations.

Evidence for the efficacy of sucrose in preterm and term infants. In preterm, term and older infants, sweet tastes are preferred over fats, proteins, lactose and water (Blass & Ciaramitaro, 1994; Graillon et al., 1997). Measured by intake, sucrose preference was related to sweetness in all age groups (Blass & Ciaramitaro, 1994). When scaled in comparison to other sweeteners, fructose is 1.7, glucose is 0.75, maltose is 0.33, and lactose is 0.6 times as sweet as sucrose (Sweetman, 2002). The calming effects of sucrose are believed to be related to endogenous opioid mediation and non-opioid systems (Blass & Hoffmeyer, 1991). Rank ordering of sugars by adults and neonates were identical, with sucrose preferred over fructose, glucose and lactose in that order. Similar to animal models, adult, term and older neonates ingest sweets or fats over non-sweets during stressful situations. This relationship may indicate opioid mediation. Behavioral
responses to non-sweet tastes are similar across age groups and include raised cheeks and narrowed or tightly closed eyes, wrinkled nose, and eyebrows pulled together (Rosenstein & Oster, 1988). Responses to sweet tastes include facial relaxation, hand-mouth behaviors and sucking behaviors.

Three systematic reviews have addressed the efficacy of sucrose for the relief of procedural pain in neonates (Stevens & Ohlsson, 1998; Stevens et al., 2001b; Stevens, Yamada et al., 2004). The reviews suggest the majority of the research on the efficacy and safety of sucrose as a pre-procedural analgesic for infants at thirty-two to thirty-four weeks’ gestation with a birth weight of 1650 – 2100 grams is inconclusive. Stevens’ et al. (2004) analysis of the studies found the methods of randomization and blinding were not clearly delineated, results were imprecisely reported or non-extractable for meta-analysis. Small samples prevented the detection of significant effects or failed to answer the research question.

In the first review, Stevens and Ohlsson (1998) obtained data from published randomized controlled trials (RCTs) where term and preterm infants received sucrose for a heel lance or venipuncture. The primary outcome was the proportion of crying time three minutes after the painful stimulus. The proportion of crying time was highest in the groups of neonates who received 0.18 grams of sucrose or water. For infant’s receiving 0.24 grams, 0.48 grams, 0.50 grams and 1.0 grams of sucrose, the proportion of crying time was significantly lower. Sucrose concentrations greater than 0.24 grams given by a syringe or pacifier approximately two minutes prior to the painful stimulus were the most effective in diminishing proportion of cry. There was no clinical benefit to administering doses greater then 0.50 grams. No adverse effects were reported with the administration
of sucrose via syringe or pacifier. While there were no differences in crying time between preterm and term neonates, preterm neonates were significantly underrepresented in the meta-analysis.

In the second review, Stevens et al. (2001b) identified fifteen studies that examined the safety and efficacy of sucrose for relieving procedural pain in the neonate. The studies were assessed, utilizing the methods of the National Collaborative Review Group. No two studies measured the same physiologic and/or behavioral outcomes. Additionally, a variety of painful procedures (e.g. heel lance, venipuncture, intramuscular injections) were utilized for the painful stimulus. Decreased concentrations of sucrose solutions of 12 gm appeared to have an analgesic effect. Doses ranging from 0.05 ml of 12 gm to 2 ml of 50 gm sucrose were used with efficacy. These variations restrict the studies’ utilization in a meta-analysis. The resulting systematic review could not identify an optimal dose for the relief of procedural pain or provide data for the safety and efficacy of sucrose for preterm, very low birth weight, unstable and/or ventilated neonates.

In the most recent systematic review, Stevens (2004) included studies that examined pain response in preterm, term, and infants less than twenty-eight days of age. The findings established that sucrose in a wide variety of doses (0.012g to 0.12g) was generally effective in decreasing physiologic heart rate and behavioral indices (crying, facial action) for pain. When infants were given sucrose, pain scores were significantly reduced. Studies included in the analysis found sucrose effective for reducing procedural pain from a single painful event.
Separate studies (Gibbins et al., 2002; Johnston et al., 1999; Johnston, Stremler et al., 1997; Stevens, Johnston, Franck et al., 1999), found that small doses of sucrose (0.12g) reduced composite pain scores comprised of heart rate, respiratory rate and facial expressions in neonates less than thirty-four weeks’ gestation. The reduction in the doses of sucrose is not efficacious in term neonates and does not appear to be sustained in older neonates. The majority of the research utilizing sucrose as a pre-procedural analgesic examined infants thirty-four to forty-two weeks’ gestation; sucrose dosing in infants two to four months of age has not been established. Further research on volume and dose-response for a wide range of infants is justified.

Johnston et al. (1999) found that repeated doses of sucrose were efficacious in diminishing procedural pain in preterm infants with a mean gestational age of thirty-one weeks; however, the analgesic effect was lost four minutes after the initial dose and two minutes after the second dose for the repeated group. Johnston et al. (2002) examined the effect of repeated doses of sucrose in infants born under thirty-one weeks’ gestation. Their findings suggest a greater frequency of sucrose dosing may generate lower scores on the Neurobehavioral Assessment of the Preterm Infant at thirty-two weeks’ postnatal age.

Comparing animal models with human neonates, Lieblich et al.(1983) determined that high levels of endogenous opioids appeared to alter responsiveness to morphine. Blass and Ciaramitero (1994) examined human neonates born to mothers who were maintained on methadone during their pregnancy to draw comparisons between endogenous opioids and responsiveness to sucrose. Their findings revealed neonates of mothers exposed to methadone were not calmed by sucrose; furthermore, the
administration of sucrose did not have a calming effect on the neonates when a pacifier to promote non-nutritive sucking was removed from their mouth. Neonates of mothers maintained on methadone avidly received the intraoral sucrose; however, they only stopped crying when the pacifier was returned to their mouth or the neonate’s hand was placed in his/her mouth. Similar to animal models, chronically high levels of methadone appears to alter the responsiveness to sucrose. A possible explanation may be that the NNS soothed neonates whose mother’s were on long-term methadone because the non-opioid pathways were intact.

Fernandez et al. (2003) examined electroencephalographic (EEG) activity, heart rate activity, and infants' facial behaviors before and after a noxious, but noninvasive, procedure. Thirty-four newborns in a RCT were administered 2 ml of water or sucrose solution before the heel stroke. Frontal EEG asymmetry scores and power in the 3 to 6 Hz frequency band were analyzed. Infants who received water showed a pattern that typifies negative affect, increased relative right frontal EEG activation from baseline to the post-heel stroke. The EEG of infants in the sucrose group remained unchanged. Heart rate increased in both groups during the heel stroke phase; however, after the heel stroke, the heart rate of infants who tasted water remained elevated, whereas the heart rate of infants who received sucrose returned to baseline. During the heel stroke, the infants in the water group exhibited a 2x longer duration of crying and grimacing compared to the infants in the sucrose group. While these findings do not support the premise that sucrose decreases pain in infants, the findings add to the growing literature demonstrating sucrose’s ability to attenuate newborns' negative responses to aversive or noxious stimuli and decreases stress and distress in newborns.
Evidence for the efficacy of sucrose in postnatal infants. Studies involving healthy and stable postnatal infants have conceptual and methodological limitations. Few studies conceptually define pain or provide a scientific rationale linking pain to the outcomes of interest. If previous studies reported outcomes reflect the investigators’ conceptualization of pain, it can be assumed that the investigators considered proportion, percentage or duration of crying to be the most valid indicator of pain in neonates (Allen et al., 1996; Barr et al., 1995; Lewindon et al., 1998; Ramenghi et al., 2002; Reis et al., 2003). No investigator used a composite pain assessment or multidimensional approach to pain measurement that represents a more comprehensive conceptualization of pain. Although research on infant cry has delineated certain cry characteristics such as pitch, intensity, melody and harmonics as being good indicators of pain (Fuller, 1991), these characteristics were not assessed with the administration of oral sucrose. Cry duration may give some indication of distress. Alone, however, it does not necessarily confirm or deny infant pain (Stevens et al., 2001b; Stevens, Yamada et al., 2004). Recent research suggests that a multivariate approach or composite pain score including physiologic, behavioral and contextual indices is a more valid measure of pain in infants (Stevens & Ohlsson, 1998; Stevens et al., 2001b; Stevens, Yamada et al., 2004).

Previous postnatal studies investigating young infants’ responses to immunizations provide variable details about the intensity, duration or frequency of the painful stimulus. Additionally, the concentration and delivery method of sucrose (syringe dropper, pacifier) was variable between studies. Barr et al. (1995) administered one injection, at two and four months, after the infants received a 50% sucrose solution by pipette. Ramenghi et al. (2002) administered two immunizations, at two, three and four
months, after the infants received a 25% or 50% sucrose solution by syringe (no NNS). Allen et al. (1996) provided two immunizations at two months and three immunizations at four months and utilized a 12% sucrose solution by syringe. Reis et al. (2003) administered four injections at two months after delivering 10 ml of 25% solution through the infant’s bottle. Of interest is the study conducted by Lewindon et al. (1998)(1997). The infants in their study received their oral polio immunization, followed by a 75% sucrose solution by syringe, and then the two routine immunization injections. The sucrose concentration used in the oral polio vaccine, administered before the 75% sucrose solution, had a sucrose/vaccine concentration of 53.5% (Barr et al., 1995) affecting the total concentration of sucrose the infant received. Today the oral polio vaccine is available for pediatric use only in special circumstances. An inactive polio injection replaced the oral polio immunization in January 2000.

Behavioral state, preparation for procedure, and soothing interventions throughout the procedures may provide comfort to the infant and act as co-interventions. These were not addressed in previous studies. Non-nutritive sucking with a pacifier contributes to reducing pain-elicited distress (Campos, 1994). The recent study by Reis et al. (2003) advocated the combination of oral sucrose, non-nutritive sucking, and parental holding to reduce the pain of infant immunization injections.

Hatfield (2005) examined the analgesic properties of oral sucrose during routine immunizations for infants at two and four months of age. The treatment group (sucrose, n=38) and control group (sterile water, n=44) displayed increasing behavioral pain responses from baseline at two, five and seven minutes. Compared to the control group, the treatment group had significantly lower behavioral pain response at two minutes.
Behavioral pain response exceeded a moderate amount at two minutes in the control group and at five minutes in the treatment group. Between seven and nine minutes, the treatment group’s behavioral pain response decreased significantly more than that of the control group (p<0.003).

Immunization administration was a limitation of the study (Hatfield, 2005). Infants generally receive three to four serial immunizations a visit during the first months of life. The administration of a single immunization two minutes after the administration of sucrose is not an accurate representation of the clinical immunization procedure. Hatfield’s study was innovative in that it utilized a composite measure of pain. It had a controlled method of delivery of oral sucrose or sterile water and controlled for the effect of dose and parental soothing on behavioral pain response during the immunizations.

Clinical toxicology. The systematic review and the meta-analysis provided support for ongoing research for the safety and efficacy of sucrose. Although no adverse effects of sucrose were reported in any of the studies described above, it is not clear whether the investigators monitored for adverse effects or if they did, for how long. One study (Willis, Chabot, Radde, & Chance, 1997) hypothesized that a 20% sucrose concentration could predispose preterm infants to necrotizing enterocolitis (NEC). Small concentrations of 20% sucrose were mixed with calcium lactate and delivered directly into the stomach eight to twelve times a day. The authors suggested that the hyperosmolarity of the sucrose resulted in local trauma to the upper gut wall with initiated the pathological process resulting in NEC.
Johnston et al. (2002) examined the effect of repeated doses of sucrose analgesia on neurobehavioral development during the first week of life in neonates younger than thirty-one weeks’ gestation. Although there were no differences between the groups on either neurobehavioral developmental outcomes or severity of illness outcomes, there were significant dose-related effects within each group. Infants were randomly assigned to a sucrose or sterile water group. In the sucrose group, higher doses of sucrose predicted lower scores on motor development, vigor, alertness and orientation at thirty-six weeks’ gestation, and lower motor development and vigor at forty weeks’ gestation. While the sample size was inadequate (n=107) in terms of the relative colinearity of the variables of interest, Johnson’s study suggests that repeated doses of sucrose in infants less than thirty-one weeks’ gestation may put infants at risk for poorer neurobehavioral development and physiologic outcomes. It is possible that infants greater than thirty-two weeks’ gestation receive greater benefit from routine use of sucrose analgesia.

A secondary analysis of Johnston et al.’s (2002) study examined physiologic stability after repeated sucrose administration. Boyer, Johnston, Walker, Filion, and Sherrard (2004) used pulse rate variability and salivary cortisol levels to estimate the physiologic stability of infants born at less than thirty weeks’ gestation after receiving repeated doses of 24% sucrose. Measures of central tendency did not differ among groups for pulse rate or cortisol levels. Franck et al., (2000) reported no difference in preterm infants when norepinephrine or vagal tone index was utilized to measure response to morphine analgesia. Vagal tone index and norepinephrine are considered sensitive indicators of physiologic stability. It is possible that pulse rate variability and salivary cortisol levels are not sensitive enough to measure physiologic stability in this group of
infants. Findings from this study suggest that treating procedural pain with repeated doses of sucrose does not promote physiological stability. Further study is required to identify outcomes and establish selection criteria for infants utilizing sucrose.

Consequences of Untreated Pain in Preterm Infants

Short Term Consequences of Pain

Failure to recognize and treat pain may lead to serious and adverse consequences for preterm infants (Anand, 1995; Anand & Hickey, 1987, 1992; Fitzgerald & Shortland, 1988). These consequences may be classified as short and long-term. Documented short-term consequences of painful procedures include increased levels of plasma cortisol, catecholamines, aldosterone, glucagon, and growth hormone (Anand et al., 1985; Anand & Hickey, 1987), decreased oxygen saturation (Van Cleve, Johnson, Andrews, Hawkins, & Newbold, 1995; Williamson & Williamson, 1983), and significantly lower partial pressures of oxygen (Rawlings, Miller, & Engle, 1980). Other short-term consequences include increased heart rate (Johnston, Stevens, Yang, & Horton, 1995; Randich & Maixner, 1984; Van Cleve et al., 1995) and rapid fluctuations in intracranial pressure (Rawlings et al., 1980). These responses deplete the already limited energy stores of the infant and increase the risk of morbidity and mortality (Anand et al., 1985; Anand & Hickey, 1987; Johnston et al., 1995).

Physical and psychologic stress, such as that associated with pain in humans, produces generalized depression of the immune system and increased susceptibility to infections (Anand, 1993; Weatherstone, Franck, & Klein, 2003). Immune system depression in infants deserves attention because of the relative immaturity of their
immune system and lack of immunoglobins, energy reserves, and previous exposure to infectious agents (Anand, 1993; Coe, Rosenberg, & Levine, 1988; Puri & Reen, 1985). Global immune response immaturity remains poorly understood in newborns. Indeed, some functions are compatible with adult levels (neutrophil ingestion and eradication of pathogens), whereas others (such as chemotaxis) are reduced. Rassmusen (2000) correlated reduced neutrophil counts with increased intensity of pain in term infants undergoing circumcision. Interaction between these two systems contributes to the increased incidence of nosocomial infection.

Long Term Consequences of Pain

Although the results of the studies are somewhat inconsistent, there is some evidence to suggest that early pain responses influence later pain behaviors. Long-term consequences of pain for infants are related to the plasticity of the nervous system. The developing infant nervous system is in a critically vulnerable period of growth from gestational weeks twenty through the first eighteen to twenty-four months of life (Anand & Hickey, 1987). This period is characterized by dendritic arborization, axonal growth, peak synaptogenesis, myelination, gliogensis, and maturation of the mechanisms and structures involved in synaptic neurotransmission (Burns, 2002; Dobbing, 1971; Dobbing & Sands, 1979). The effect of pain will vary with the level of development (Reynolds & Fitzgerald, 1995; Teng & Abbott, 1998).

Data extrapolated from animal models suggest that neonates exposed to noxious stimuli develop permanent structural and functional reorganization of the central nervous system resulting in alterations to future pain responses as adults (Anand, 1993; Fitzgerald, 1993; Plotsky et al., 2000; Reynolds, Alvares, Middleton, & Fitzgerald, 1997;
Ruda et al., 2000) reported that skin wounds inflicted on rat pups on the day of birth (P0) caused decreased pain thresholds resulting from hyperinnervation in the injured area that lasted three months after the painful event. This hyperinnervation was accompanied by a greater magnitude of nerve sprouting in the area of injured skin, and it lasted longer than that which occurred in rats that were seven to fourteen days of age at the time of the skin injury (Reynolds & Fitzgerald, 1995).

Several forms of permanent structural changes to the brain and spinal cord have been identified in animals. First, rats subjected to recurrent pain (injections into the left hind paw) from post natal day one (P1) developed widespread increase in neural excitability within the spinal cord which resulted in an expansion of their cutaneous receptive fields, a significant loss of neurons in their dorsal horn, and a decrease in nociceptive primary afferent neurons compared to control rats (Ruda et al., 2000). These rats, as adults, exhibited increased responses to noxious and non-noxious stimuli relative to the control rats. In human preterm infants, prolonged cutaneous sensitivity and hyperalgesia that lasted for days and weeks has been shown after repeated heel lance procedures (Reynolds & Fitzgerald, 1995). Second, severance of a single peripheral nerve in neonatal rats results in the death of a majority of the dorsal root ganglion cells, which stimulates nearby central dorsal root terminal nerves to sprout functional connections with inappropriate dorsal horn cells well outside their normal area of termination and to occupy space normally reserved for the deafferentated nerve (Fitzgerald, 1991b; Fitzgerald & Shortland, 1988). This distortion is permanent and is not limited to the primary afferent nerves. Abnormalities spread to postsynaptic dorsal horn cells and on to higher of levels including the pyramidal tract and cortex (Chimelli & Scaravilli, 1985;
Cook, Woolf, Wall, & McMahon, 1987; Dawson & Killackey, 1985; Kaas, Menenich, & Killackey, 1983; Shortland & Fitzgerald, 1994). The somatosensory cortex is reorganized after peripheral nerve injuries in both adult and developing mammals (Kaas et al., 1983). Repeated stimulation of the forearm in newborn kittens resulted in a permanent 30% increase in the number of dendritic intersections and generally enlarged growth of dendritic trees in the cortex area associated with the stimulated forearm as opposed to the non stimulated forearm (Spinelli, Jensen, & Viana Di Prisco, 1980).

Anand et al. (1999) found that in addition to the physiological and structural changes associated with repetitive pain, pain behaviors were also altered. Newborn rat pups that received repetitive painful stimuli four times a day for seven days had decreased pain thresholds as compared to rat pups that did not receive repeated pain (control). Furthermore, the adult rats receiving repeated pain stimuli demonstrated increased anxiety states, increased preference for alcohol to decrease anxiety, social defensiveness, stress-related behaviors such as freezing or digging, and learned helplessness. The connection between repeated painful experiences in human infants and anxiety, social defensiveness, learned helplessness, and preference for alcohol has not been documented; however, these studies suggest the painful experiences of infants in the neonatal intensive care unit may have long-lasting consequences on both the structure and function of their brains.

Repeated painful procedures may lead to long-term sensory, behavioral, psychological and emotional consequences. Long-term consequences identified in the literature include the following:
A decreased sensitivity to the commonplace pain of childhood (Grunau, Whitfield et al., 1994a). The sample for this study consisted of parents of 124 infants born at less than 1,001 grams who had now reached eighteen months of age. Parents were asked to rate their child as "very sensitive to the pain of bums or cuts or other common hurts" (Grunau, Whitfield, Petrie et al., p. 342) on a scale from 1 to 5 in which 1 equaled not very characteristic and 5 equaled very characteristic of their child. Parents of these infants rated their children as significantly (p < .005) less sensitive to pain as compared with the control group.

A higher incidence of somatic complaints and somatization of unspecified origin (Grunau, Whitfield, & Petrie, 1991; Grunau, Whitfield et al., 1994b). A prospective sample of thirty-six children who were born at less than 1,001 grams (extremely low birth weight [ELBW]) and thirty-six matched full-term controls were studied at 4 ½ years of age. The somatization questions on the Personality Inventory for Children revealed significantly higher somatizations, such as somatic complaints of undetermined origin, compared with children who were full-term at birth. The length of stay in the neonatal intensive care unit was correlated with increased somatization scores. Only the ELBW children had somatization scores high enough to necessitate clinical concern (Grunau, Whitfield et al., 1994b).

Changes in patterns of responses to painful stimuli after repeated exposure (Johnston et al., 1996)

In preterm neonates, the threshold for flexor withdrawal reflex is reduced with repeated heel lances (Fitzgerald et al., 1989; Fitzgerald, Shaw et al., 1988).
Compared to the intact contralateral heel, the injured heel had a lower withdrawal reflex. Similarly, Andrews and Fitzgerald (1994) compared the flexor withdrawal threshold in infants with ischemic leg injuries. Higher withdrawal thresholds where observed in the contralateral healthy leg.

Johnston et al. (1996) compared pain responses of neonates who were thirty-two weeks’ post-conceptional age (PCA) (born at twenty-eight weeks’ gestation and hospitalized in a NICU for four weeks) to neonates who were born at thirty-two weeks’ gestation. Neonates were observed during a routine heel lance for the presence of pain indicators, heart rate, oxygen saturation and three facial actions (brow bulge, nasolabial furrow and eye squeeze). Neonates at thirty-two weeks’ PCA had significantly higher heart rates ($F = 25.13, p< 0.001$) and significantly lower oxygen saturation ($F = 20.14, p< 0.001$) than neonates born at thirty-two weeks’ gestation. In contrast, the neonates at thirty-two weeks’ PCA had significantly less eye squeeze ($F = 9.85, p< 0.002$) and attend towards less nasolabial furrow ($F = 3.32, p< 0.076$) than neonates who were born at thirty-two weeks’ gestation. A stepwise regression analysis was undertaken with Apgar score, weight at birth and at data collection, severity of illness at the time of data collection, post conceptual age, and total number of invasive procedures. Results of the analysis revealed that the number of painful procedures the neonate had experienced prior to the painful procedure being evaluated explained most of the variance in facial expressions. Apgar scores and birth weight influenced variance in physiological responses.
Taddio et al. (1995) examined post hoc analyses of previous data to determine the effectiveness of Eutectic Mixture of Local Anesthetics (EMLA) for relieving procedural pain associated with immunization. Males circumcised within two days of birth cried significantly longer (53 vs. 19 seconds, \( p = 0.02 \)) and displayed higher pain intensity scores as measured on the Visual Analogue Scale (VAS) (8 vs. 6, \( p = 0.01 \)) at immunization at two months of age than males who were not circumcised. The findings were determined on a small sample size (\( n = 42 \)) and visual analogue scale reports by health professionals who were not blinded to group allocation. Actual assessment of the neonate's pain response, based on physiologic or behavioral indicators was not conducted. Taddio et al. (1997) later reported in a double-blinded, randomized, controlled trial that male neonates (\( n = 68 \), alpha .80) who received EMLA prior to circumcision decreased their facial activity (12 to 24%, \( p < 0.001 \)) and heart rate (10 beats/min, \( p < 0.007 \)) compared to male neonates who did not receive EMLA.

Porter et al. (1999) conducted a cross-sectional and longitudinal study with neonates of different gestational ages and postnatal ages (\( n = 152 \)) and found that the magnitude of physiologic and behavioral responses in preterm and term neonates increased with increasingly invasive procedures. Age was not a factor in the neonate’s agitated response to increasingly painful procedures. In the first week of life, there was not a significant interaction with pain responses between gestational age and PCA; however, after preterm neonates reached thirty-six weeks’ PCA, the magnitude of their physiological responses differed from neonates born at term. Compared with all other gestational age groups, neonates
born closer to term displayed smaller heart rate increases to procedures. Neonates less than twenty-eight weeks’ gestation, who were thirty-six weeks’ PCA, displayed the most variability. The findings support Johnson et al.’s (1996) study; however, Porter et al. did not find behavioral differences between preterm and term neonates.

- Self-regulation behaviors may be affected by early chronic stress such as that experienced in the neonatal intensive care environment. A tonic negative affect that may inhibit the development of integrative self-regulation is a reported consequence of overly stressful situations (Anand & Scalzo, 2000; Mcgrath & Craig, 1989; Ryan, Kuhl, & Deci, 1997; Wilson & Gottman, 1996).

- Emotional or psychiatric disorders. Emotional and psychiatric disorders observed in children who were born preterm include the act of seeking painful experiences for pleasure, increased anxiety, and social defensiveness (Aisenstein, 1987; Hertzog, 1983; Tyson, 1984).

In human preterm infants, significant differences (p < .001) in regional brain volumes have been shown in comparison with normal full-term infants (Bhutta & Anand, 2002; Peterson et al., 2000). The study data indicated that preterm birth is associated with regionally specific long-term reductions in brain volume and that poorer cognitive outcomes were associated with these morphologic abnormalities. Among the specific regions that were smaller were the sensorimotor, amygdala (up to 30%), hippocampus, corpus callosum, premotor, midtemporal, parieto-occipital, and cerebellum. Brain volumes in the preterm infants were significantly larger than the controls in two areas: the occipital and temporal horns of the ventricles (Peterson et al.).
Little empirical data pertaining to the long-term consequences of pain in human infants exist. Animal data suggests that prolonged exposure to pain alters physiologic and biobehavioral responses resulting in permanent shifts in autonomic arousal states. Human studies, however, have yielded conflicting results. Inconsistent findings and lack of methodologic rigor in some of the earlier studies require further study to establish long-term differences in pain responses.

Chapter Summary

Appropriate pain management strategies depend on accurate assessment of the infant’s physiologic and behavioral pain cues in the context of their developmental and behavioral states. Management of procedural pain for infants has been limited by the misconceptions that infants do not experience pain. Anand and his colleagues (1987) have provided evidence that infants have the neurological anatomy and physiological development to perceive and respond to painful stimuli approximately at mid-gestation. Studies supply sufficient evidence to support the belief that infants have physiological (Craig et al., 1993; Field & Goldson, 1984; Grunau, Whitfield et al., 1994b; Stevens & Johnston, 1994) and behavioral (Horii & Fuller, 1990; Johnston & Strada, 1986; Lester, 1987; Michelsson, Sirvio, & Wasz-Hockert, 1977b; Owens & Todt, 1984; Porter et al., 1986) responses to tissue-damaging stimuli. Moreover, immature descending pain pathways result in a greater magnitude and a prolonged duration of pain for infants.

The short-term responses of untreated pain in the preterm infant include physiologic, behavioral, and facial expressions of pain that enable caregivers to assess pain. Long-term consequences of painful procedures may result in permanent structural
changes in the nervous system (Anand, 2000a; Anand et al., 1999; Anand, Grunau, & Oberlander, 1997; Anand & Scalzo, 2000; Porter et al., 1999). The long-term effect of pain varies with the level of development (Reynolds & Fitzgerald, 1995; Teng & Abbott, 1998). Long-term sensory consequences include decreased sensitivity to the commonplace cuts and injuries of childhood and higher incidence of somatic complaints of unspecified origin (Grunau et al., 1991; Grunau, Whitfield et al., 1994b; Grunau, Whitfield, Petrie et al., 1994; Holsti et al., 2002). Conflicting results with animal studies and lack of study replication warrant that these results be interpreted with caution until there is more definitive evidence from studies in human infants. Emotional and psychiatric disorders observed in children who were born preterm include the act of seeking painful experiences for pleasure (Aisenstein, 1987).

The acknowledgment that human neonates and infants perceive pain has expanded the domain of pain management and has led to a heightened effort to relieve infant pain (Anand & Hickey, 1987). Further studies have indicated that infants are particularly vulnerable to the detrimental effects of pain (Anand, 1990; Anand & Craig, 1996; Carraccio et al., 1996; Fitzgerald, 1991a, 1993; Lieblich et al., 1983). To date, the evidence supporting the relationship between painful procedures and future pain responses remains unclear.
CHAPTER 3
METHODOLOGY

The purpose of this randomized clinical trial was to investigate the analgesic effects of intra oral sucrose on repeated painful procedures (three serial routine immunizations) in infants at two and four months of age. The primary aims of this study were to establish the analgesic effectiveness of intraoral sucrose during routine immunizations in infants at two and four months of age and to identify the age-related changes in the analgesia of intraoral sucrose. Findings from this study will make important contributions to research on the analgesic potential of oral sucrose. The development and testing of the proposed methodology will have far-reaching implications for designing studies to explore the benefits of oral sucrose as a pre-procedural intervention for other painful episodes and as an adjunctive treatment to maximize analgesia for more prolonged and severe pain states in infants and children.

Research Questions

Primary Research Question

Will sucrose decrease behavioral pain response during routine immunizations in an infant at the two and four month well-child visit?

Second Research Question

After sucrose administration, will there be age related change in behavioral pain response during routine immunizations in an infant at the two and four month well-child visit?
Specific Aims

Primary Research Question

Using an observational pain scale, in infants at two and four months of age, compare the analgesic effects of a 24% intraoral sucrose solution, 0.6ml/kg (0.3ml/lb) in an infant to the administration of a volume equivalent solution of sterile water. Each solution will be delivered two minutes prior to three serial routine immunizations via a syringe onto the infant’s tongue while the infant is simultaneously sucking on a pacifier.

Second Research Question

Using an observational pain scale, in infants at two and four months of age, compare the age-related changes in behavioral pain responses in an infant after the administration of a 24% intra oral sucrose solution, 0.6ml/kg (0.3ml/lb) to the behavioral pain responses after the administration of a volume equivalent solution of sterile water. Each solution will be delivered two minutes prior to three routine immunizations via a syringe onto the infant’s tongue while the infant is simultaneously sucking on a pacifier.

Hypothesis

Primary Research Question

In infants at two and four months of age, a 24% intra oral sucrose solution, 0.6 ml/kg (0.3ml/lb) and non-nutritive sucking will significantly decrease the objective measures of acute pain during three serial routine immunizations, compared to a volume-equivalent dose of a sterile water control solution and non-nutritive sucking.
Second Research Question

In infants at two and four months of age, after the administration of a 24% intraoral sucrose solution, 0.6 ml/kg (0.3ml/lb) and non-nutritive sucking, there will not be an age-related change in behavioral pain responses during routine immunizations at the two-month and four-month appointment compared to behavioral pain responses after administration of a volume-equivalent dose of a sterile water control solution and non-nutritive sucking.

Study Design

To control the application and scheduling of treatments, ensure homogeneity, and facilitate causal inference, a longitudinal, randomized, investigator and parent-blind, equivalency clinical trial was proposed to study the analgesic effects of oral sucrose during three serial routine immunizations (Anand, 1993; Raju et al., 1980; Shadish, Cook, & Campbell, 2002). The target population consisted of all infants two to four months in age. The study population was term neonates (thirty-seven to forty-two weeks' gestation), postnatal age maximum nineteen weeks (133 days) presenting for care at a university-affiliated pediatric ambulatory care clinic.

Masking

Evidence-based literature supported the analgesic properties of sucrose and the calming effects of NNS. It was unethical to deny infants interventions to diminish pain; therefore, the control group received sterile water and a pacifier to facilitate NNS. The intervention group received the 24% sucrose solution and the provision of NNS with a pacifier. The sucrose solution was a commercial, sterile, unit dose solution (11ml/cup
with a peel-off lid) marketed as Sweet Ease™ and manufactured by Children's Medical Ventures. Both solutions were clear, non-odorous, similar in physical characteristics (texture), and not visibly distinguishable in any other way.

Threats to Internal Validity

Potential confounders were addressed in the design of the randomized control trial. Threats to internal validity included the number of invasive procedures performed between the infant's birth and data collection. Every attempt was made to recruit and randomize infants during their newborn appointment. Data collection occurred after randomization during the infants’ two and four-month appointments. The primary outcome measure, acute procedural pain, was determined by using a validated multivariate measure (Soetenga et al., 1999). The PI was blinded to the treatments and documented the primary outcome measure, acute procedural pain.

The routine immunizations and their order of administration were consistent throughout the study period. Demographic information such as date of birth, gestational age, postnatal age, gender, birth weight, current weight, type of delivery, parity, previous painful experiences (circumcision, lab draws) and prior analgesic use was verified for accuracy by parents. Attrition occurred if parents withdrew their consent after the administration of the solution.

Sample

Following ethical approval by the Institutional Internal Review Board (IRB) for the study of human subjects, written parental or legal guardian (caregiver) consent was obtained for each infant’s study participation. A convenience sample of eligible infants
was identified from a consecutive series of patients who visited the ambulatory pediatric clinic for routine immunizations at two and four months of age. Pediatricians, pediatric nurse practitioners and clinic nurses notified the PI of potential participants from the appointment records of the pediatric ambulatory care clinic.

Inclusion Criteria

Infants were eligible for entry into the study if their:

1. Two and four month well-child visit was scheduled at the study site
2. Gestational age at birth was between thirty-seven and forty-two weeks completed gestation
3. Birth weight was greater than 2.5 kg
4. No evidence of acute or chronic disease processes

Exclusion Criteria

Infants were ineligible for entry into the study for the following reasons:

1. Concurrent illness
2. Infant has been introduced to solid food
3. Infant would not receive a pacifier
4. Infant was diagnosed with a major congenital disorder which would alter behavioral response to painful stimuli (e.g. cerebral palsy)
5. Language barriers precluded the process of obtaining parental consent
6. Parents wished to
   a. Provide an analgesic/sedative six hours prior to immunizations (participating parents who wish to administer acetaminophen as
prophylaxis against adverse reactions were asked to delay administration until after the immunizations)

b. Breast feed 30 minutes prior to immunizations or breast feed during immunization

**Sample Size Calculation**

The primary outcome of acute pain response was used to calculate the sample size. Comparison of mean pain scores from the University of Wisconsin Children’s Hospital (UWCH) pain scale was utilized to determine a decrease in acute pain response. During a painful procedure, acute pain response decreased from 2.58 (SD = 1.05) to 0.51 (SD = 0.65) in a control versus a treatment group (Soetenga et al., 1999). No Bonferroni correction to account for multiple comparisons was stated. Soetenga et al. also examined contrasts between groups. There was a significant difference between groups when analyzed by ANOVA (F= 80.82, p=0.001). Data from these studies suggest that a reduction of 2 points on the UWCH pain scale (approximately 20% on mean observed scores) is considered clinically significant. Harrison, Johnston, and Loughnan (2003) reported a 20% reduction in mean facial expression pain scores as clinically significant.

A sample size calculation of thirty two infants (sixteen infants per treatment group) is based on a power calculation using a two by two repeated measures ANOVA with alpha at 0.05 (two-sided), standard deviation 1.2, with statistical power of .80 to detect a treatment difference (reduction of 20 percent in UWCH scores between the two interventions) with a baseline and two serial measures of pain. The randomized sample was stratified and equally divided among the two treatment and age groups. Each infant would participate in the study at two points, their two-month well child visit and their
four-month well child visit. IRB approval (Appendix B) included provisions for oversampling (estimated at 20%) to account for participant attrition, disenrollment or misplaced data. The adjusted sample size was forty infants, twenty infants per treatment group.

RCT Procedure

An exploratory study established the feasibility of the proposal. Recruitment, randomization and immunization procedures were successfully conducted at the proposed research site, utilizing the clinic staff and client population. Unexpected deviations from the exploratory study’s protocol were discussed with the clinic's medical director and nurse manager. The exploratory study deviations were appraised as minor and did not impact the infant’s safety or compromise the integrity of study data. The study design of the proposed research was structured such that intent-to-treat data analysis included the study procedure deviations.

Prior to Recruitment

Pediatricians received a letter requesting their support of the proposed investigation (Appendix C). Pediatricians and staff had the opportunity to attend a presentation of the study at the research site addressing the purpose, interventions, concurrent interventions, immunization sequence, data collection procedure, outcome measures, and losses to attrition. Attendees were given an opportunity to ask questions. The PI's telephone number and e-mail address was distributed to ensure that the clinic staff had adequate access to the PI for further questions.
Recruitment

The PI, physicians, nurse practitioners and clinic staff nurses identified potential participants at the pediatric ambulatory care clinic from the daily appointment schedule. The PI provided the pediatric ambulatory care administrative assistants with a letter explaining the study. The administrative assistants placed the letter in the clinic’s newborn packet, which was distributed to parents at their infant’s first visit to the clinic (Appendix D). In addition, the PI provided the pediatric ambulatory care clinic medical records assistants with a parental notification slip (Appendix E) to attach to the outside of the newborn’s chart. At the first newborn visit, the clinic nurse approached parents of infants who met the inclusion criteria and asked if they were willing to listen to an explanation of the study. If parents agreed to be approached, they were asked to provide their name and telephone number on the parental notification slip. The investigator visited or contacted the research site daily to collect the slips and answer any questions the parents or staff may have had regarding the study. The parents and staff were able to contact the PI via personal communication, telephone or e-mail.

Randomization

Randomization assignment was determined using a computer-generated randomization list created by a statistician in the Department of Health Evaluation Sciences at the Milton S. Hershey Medical Center who is not be involved in recruitment or data collection procedures. To ensure a balance over time of infants randomized to non-nutritive sucking (NNS) and sterile water with those infants randomized to non-nutritive sucking and sucrose, a computer-generated randomization list randomized infants in permuted blocks of four. Conceptually, this was operationalized by grouping
infants in blocks of four. In the first block of four, two infants were randomized to the non-nutritive sucking and sterile water group and two infants were randomized to the non-nutritive sucking and sucrose group. In the second block of four infants, two infants were randomized to the non-nutritive sucking and sterile water group and two infants were randomized to non-nutritive sucking and sucrose group. To ensure allocation concealment, progressive numeration from a randomized list enrolled eligible infants. Randomization in permuted blocks of four did not influence the scheduling of an infant's two and four month appointment. After randomization, infants did not appear for their two and four month well-child appointment in the order they were randomized.

**Infants Randomized to the Sucrose and NNS Group**

Infants in the sucrose and NNS group received 0.6 ml/kg of 24% sucrose via a syringe onto the surface of the tongue followed immediately by the insertion of a Wee Smoothie pacifier (Children's Medical Ventures, Inc. Norwell, MA, No. 96004N) into the infant's mouth. The pacifier was held in place by the parent or the clinic nurse two minutes before, during and three minutes following the immunization.

**Infants Randomized to the Sterile Water and NNS Group**

Infants in the sterile water and NNS group received the identical intervention as infants randomized to sucrose and NNS group except that they received 0.6 ml/kg of sterile water instead of 0.6 ml/kg of 24% sucrose.

**Randomization Assignment**

The PI telephoned the parents who returned the notice to potential participant slips to explain the study. If the parents agreed to participate, their child was randomized to the control or treatment group. Once randomized to an intervention group, each infant
participated in the study at two points: the two and four-month well child appointments. Thus, the study groups were independent of each other (Figure 3.1).

During the initial telephone conversation, parents were asked to supply the dates of their child's two and four-month well child appointments. At the two-month appointment, the PI met with the parents prior to their scheduled appointment to obtain informed consent (Appendix F) and collect demographic and health history data (Appendix G). The infant's chart included a copy of the informed consent and IRB abstract, informing the medical and nursing staff of the infant's participation in the study.

To assess age-related changes and the clinical effectiveness of sucrose, the same infants were assessed at two and four months. All infants received one of the two interventions as defined by the group to which they are randomized. Moreover, the same infants randomized to receive sucrose (or sterile water) at two months received sucrose (or sterile water) at four months.

**Immunization Procedures**

The procedure was identical at two and four months. Prior to the study, an advanced practice nurse in Nursing Research delivered a computer-generated randomization chart and the sucrose solution to the clinic. The randomization chart containing the forty study participants and their allocation groups was kept in a folder behind the nurse's station. At the beginning of every week, the PI informed a clinic nurse in the pediatric ambulatory clinic as to the participants involved in the study that week. After the parents checked in at the front desk, the receptionist informed the parents that the PI was waiting to see them. The PI introduced herself and escorted the parents to a private waiting area to obtain informed consent. When a room became available, a
medical assistant escorted the infant and parent to an exam room. The medical assistant obtained the infant's weight, length, head circumference and vital signs. The PI recorded the infant's weight on the data collection sheet. To protect the infant's privacy, the PI dismissed herself from the exam room until the completion of the physical exam.

After leaving the exam room, the PI calculated the volume of test solution to be administered. The infant's study participant number and volume of solution to be administered was documented on a post-it™ and placed on the counter above the refrigerator containing the vaccines. After the PI left the nursing station, a nurse at the pediatric ambulatory clinic not involved in recruitment or data collection reviewed the post-it™ for the infant's study participant number and volume of solution to be administered. She retrieved the treatment assignment (e.g. sterile water or sucrose) from the folder behind the nurse’s station and prepared the treatment or control solutions using sterile syringes according to the infant’s group assignment. Preparations were indistinguishable in order to blind the PI and parents to treatment allocation.

After the physical exam, the PI and the clinic nurse entered the examination room. A baseline pain assessment was obtained prior to the administration of the treatment or control solution. Two minutes following the administration of the treatment or control solution, three serial routine immunizations were administered. The order of the immunizations was consistent throughout the study period. The first immunization was the combined diphtheria, tetanus, pertussis, polio, and hepatitis B (DTaP, IPV, and Hep B) vaccine; the second was the Haemophilus influenzae type b (HIB) vaccine; and the third was the pneumococcal conjugate (PCV7) vaccine. Two additional pain assessments were performed. The second pain assessment occurred immediately after the three
immunizations were administered (two minutes after the administration of the treatment or control solution). The third pain assessment occurred three minutes after the second pain assessment (five minutes after the administration of treatment or the control solution). The injection schedule, pain assessment schedule and study procedures were as follows:

1. Baseline: To insure a calm state before the intervention, caregivers supported the infants comfortably in their lap or placed them in a supine position on the table for five minutes. When the infant was in a calm state, a baseline measure of pain was documented using the UWCH, (Soetenga et al., 1999). Caregivers were instructed not to cuddle or swaddle their infant immediately after each immunization.

2. Intervention (duration one minute): The treatment or control solution was syringed onto the infant’s tongue for one minute while the infant sucked on a pacifier following clean technique. The infant was encouraged to suck on a pacifier by gently moving the pacifier in and out of the mouth. After the infant received the treatment or control solution, the PI activated a kitchen timer. The timer measured seconds beginning at zero.

3. Stimulus/Immunizations (three minutes into the procedure): The principle investigator and clinic nurse monitored the kitchen timer. Two minutes after administration of the solution, the infant received the three scheduled routine immunizations (the combined DTaP, IPV, and Hep B injection, the HIB, and the PCV7). The immunization procedure was as follows: the clinic nurse cleansed the left thigh with alcohol and administered the combined injection.
Immediately following the combined injection, the right thigh was cleansed with alcohol and the HIB vaccine was administered into the right thigh followed by the PCV7 in the right thigh. The infant’s greatest response during the immunization procedure determined the behavioral pain response score. Documentation of the second pain score occurred immediately following the PCV7 injection.

4. Recovery (six minutes into the procedure): Five minutes after the administration of the treatment or control solution, the third pain and final assessment measure occurred.

Figure 3.2 summarizes the immunization procedure.

All vaccine preparations were of the same commercial brand. Pediarix supplied the combined DPaT, Hepatitis B and inactive polio vaccine, Aventis Pasteur supplied the haemophilus B conjugate vaccine, and Wyeth supplied the pneumococcal 7-valent conjugate vaccine. All infants received their immunizations with the same disposable needle gauge and length, 25-gauge and 5/8-inch length. Once the injection and pain assessment procedures were completed, no additional study care or monitoring was required.

**Intervention**

*Sucrose*

Sucrose was operationally defined as a 24 % disaccharide solution manufactured by Children's Medical Ventures Inc., Norwell, MA. (No. 99044) The solution is employed as a treatment to calm and comfort distressed infants
Figure 3.2 Immunization Procedures by Phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Baseline</th>
<th>Intervention Complete</th>
<th>Stimulus</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calm infant</td>
<td></td>
<td></td>
<td>Immunizations</td>
<td></td>
</tr>
<tr>
<td>Administer test solution</td>
<td></td>
<td></td>
<td>Application of Dressing</td>
<td></td>
</tr>
</tbody>
</table>

| Time in Minutes | 0* | 1 | 3* | 6* |

* UWCH scores computed at 0, 3, and 6 minutes
The dose in grams is calculated by the concentration of sucrose (expressed in percent) multiplied by the volume (in ml) delivered to the infant. The recommended dose for term infants is 2 ml (Stevens & Ohlsson, 1998; Stevens, Yamada, & Ohlsson, 2001b). For the purpose of this study, an alternative dose, which considered the infant's age and developmental stage (0.6 ml/kg of 24% sucrose solution, the recommended dose derived from the meta-analysis calculated for the infant’s body weight) was administered (Stevens & Ohlsson, 1998; Stevens et al., 2001b).

**Non-nutritive sucking**

Non-nutritive sucking was operationally defined as a Smoothie pacifier (Children’s Medical Ventures, Inc. Norwell, MA No. 96004N) introduced into the infant's mouth without the presentation of breast milk or formula. The parent or clinic nurse encouraged non-nutritive sucking by introducing the pacifier into the infant's mouth without the presence of breast milk or formula and provided gentle rhythmic stimulation of the pacifier. Non-nutritive sucking was considered present when the characteristic pattern of non-nutritive sucking was observed.

**Outcome Measures**

*University of Wisconsin Children's Hospital Pain Scale*

**Description**

The University of Wisconsin Children's Hospital (UWCH) Pain Scale measured the dependent variable, acute pain response. The use of behavior observations is the primary assessment method recommended by the Acute Pain Management Guideline
Panel for the assessment of pain in infants and young children (Carr et al., February, 1993). The UWCH Pain scale is an observational instrument, developed by Soetenga et al. (1999), consisting of five behavioral parameters that demonstrate content validity for assessing pain. The instrument was specifically developed for preverbal and nonverbal children. The instrument contains five parameters: cry, facial, behavioral, body movement, and sleep, all of which are shown to change in response to pain. Researchers of infants and young children have measured cry vocalization in response to noxious stimuli, specifically the intensity, pitch, and duration of cry (Fuller, 1991; Fuller & Conner, 1995). Cry as a single measure of pain is unreliable due to its inconsistency in infants and young children; however, when used as part of a composite assessment of pain, it is considered a valid indicator (Fuller, 1991). Five facial actions from the upper region of the face are derived from the Neonatal Facial Coding System and have been shown to be sensitive and specific for pain: brow bulge, eye squeeze, and nasolabial furrow (Grunau & Craig, 1987). Infants and young children respond to noxious stimuli with whole body responses: tenseness, rigidity, jittery movements, flexion of extremities, and thrashing (Coffman et al., 1997; Fuller & Conner, 1995; Hudson-Barr et al, 1998). Consolability and sleep pattern disturbances were significantly correlated with assessed levels of pain (Fuller & Conner, 1996).

The UWCH pain scale (Soetenga et al., 1999) does not include physiologic parameters. Physiologic parameters such as heart rate, respiratory rate, systolic and diastolic blood pressure, palmar sweating, oxygen saturation, and fluctuation in intracranial pressure have been shown to change in response to pain; however, they are not reliable indicators of the presence and severity of pain in infants and young children.
(Craig et al., 1993; Porter, 1989; Stevens, Johnston, & Grunau, 1995). Physiologic indices are a better representation of a stress response (Craig et al., 1993; Fuller & Conner, 1995; Gunnar, Porter, Wolf, Rigatuso, & Larson, 1995).

**Validity**

The UWCH pain scale has content, criterion, and construct validity (Soetenga et al., 1999). External expert review established content validity. Construct validity demonstrated differences in pain scores between painful and non-painful events, and differences in pain scores before and after analgesia administration. The difference in means for painful events was non-significant. The mean (SD) rating during a procedure with standard care intervention was 2.58 (1.05); during a procedure with standard care intervention and prior to receiving pain medication, the mean (SD) was 2.63 (1.12). In contrast, the mean (SD) pain rating after receiving pain medication was 0.51 (0.65). The difference in mean pain ratings between the groups was significant ($F = 80.82, p < 0.001$). When contrasts between groups were examined, there was a significant difference between the ratings during procedures compared to ratings after analgesia administration, ($p < 0.001$). Moreover, ratings prior to receiving analgesics and ratings after analgesia administration were significant ($p < 0.001$). Criterion validity was determined by comparing ratings with those obtained on the Wong-Baker Faces scale (Wong & Baker, 1988). Correlation and paired t-test analyses established the relationship between scores on the UWCH pain scale and scores on related instruments. The correlation between the UWCH scale (Soetenga et al., 1999) and the faces scale was .62 ($p = < 0.001; n = 68$). A paired t-test between the behavioral scale ($x = 2.27, SD = 1.28$) and the faces scale ($x = 3.49, SD = 1.40$) was significant ($t = -8.53, p < 0.001$). When
parents filled out the faces scale, (n = 57), the correlation between the behavioral scale and the parent's ratings was r = .53. When nurses filled out the faces scale (n = 11), the correlation was r = .89. Parents had significantly higher ratings of child's pain (t = -8.80, p < .001) using the faces scale (x = 3.73, SD= 1.24) than nurse clinicians using the behavioral scale (x = 2.35, SD = 1.19). Nurse clinicians using the faces scale had similar ratings to nurse clinicians using the behavioral scale (x = 2.23 and x = 1.82, respectively; t = 1.70, non significant) (Soetenga et al., 1999). Cross-cultural validation of the tool has not been conducted.

**Reliability**

The correlation between raters was .92 (p < 0.001; n = 58). Correlations within categories between the two raters were .86 for vocal, .81 for facial, .82 for body movement, .78 for behavioral, and .68 for sleep. Cronbach’s alpha, for all five categories in the scale is .93 (n=72) (Soetenga et al., 1999). In some situations, such as outpatient settings, the rater could not determine the sleep pattern of the child. Cronbach's alpha for all four categories excluding sleep was .87 (n = 154).

These data establish the discriminate validity of the UWCH and suggest that the UWCH Pain scale is a reliable and sensitive measure of pain for preverbal and nonverbal children. The UWCH’s clinical utility has been established at the bedside (Soetenga et al., 1999). Jannetti Publications, publishers of Pediatric Nursing and owners of the UWCH Pain Scale copyright, has granted permission to utilize the scale.

**Scoring**

In the UWCH Pain Scale (Soetenga et al., 1999), each of five behavioral parameters is assessed in response to painful stimuli (Appendix A). Indicators in the
UWCH Pain Scale are numerically scored from baseline to stimulus along a six-point ordinal scale from zero to five. Six point scales (0, 1, 2, 3, 4, 5) reflect the changes in increasing magnitude in the behavioral indicators from baseline values. The mean of the five indicators reflect the overall score. Higher scores reflect a greater pain response. The maximum attainable score is 5. A score of 0–1 is reflects absence or minimal pain, 2-3 suggests mild to moderate pain, and a score of 4-5 indicates moderate to severe pain. Further research is required to establish the values of 2 and 4 as sensitive cut-off points for minimal versus moderate-severe pain.

Data Analysis

Interim Analysis

The safety monitoring committee, consisting of Maryellen Gusic MD, Associate Professor of Pediatrics, and Medical Director of at Penn State University Pediatric Associates Ambulatory Clinic, and Christine Arnold CRNP, a pediatric nurse practitioner, was established prior to initiation of the study. Dr. Gusic, the chair of the safety monitoring committee, was informed of each adverse event as per unit policy. For each adverse event, Dr. Gusic reviewed the infant's clinical status in relation to the event and examined the need for an interim analysis.

Stopping Rules

If interim analysis was necessary, stopping rules were employed. Stopping rules are employed with the occurrence of major adverse events directly related to the study intervention such as severe choking, coughing or vomiting following the administration of solution, or tachycardia or bradycardia requiring immediate medical intervention such
as intubation or resuscitation. No major adverse event occurred within the study; therefore, stopping rules were not employed.

**Final Analysis**

The primary question of the study was to determine the analgesic properties of a 24% sucrose solution and NNS as a pre-procedural intervention for infants experiencing routine immunizations compared to a volume-equivalent sterile water solution and NNS. The raw data were reduced and coded prior to the final analysis. Statistical analyses of the behavioral data were completed using the Statistical Analysis System (version 9.1.3; SAS Institute Inc., Cary, NC) following the intent-to-treat principle. Demographic and other baseline variables prior to randomization were compared between treatment groups, and descriptive SAS statistics were used to analyze data for normality and provide means, ranges, standard deviations and variances. Nominal, categorical and ordinal data were obtained from the demographic portion of the data collection sheet, and interval data were obtained from the UWCH scores. The distribution of UWCH scores was examined. A repeated measures analysis of variance was performed to determine the effects of treatment, age and time on the primary outcome, which was behavioral pain response measured by UWCH scores. Unless otherwise noted, p-values are adjusted using the Bonferroni procedure for multiple comparisons. A significance criterion of 0.05 was used for all statistical tests.
Human Subjects Protection

Written approval was obtained from the Office of Research Protection at University Park and from the Penn State Milton S. Hershey Medical Center’s Institutional Review Board and Human Subject Protection Office. Every attempt was made to approach and communicate with all parents of eligible infants regardless of age, race, gender, socioeconomic status or ethnic background. The PI explained the purpose of the study and procedures and obtained written informed consent. Parents were given a copy of the consent form explaining their rights and providing the telephone numbers of the PI and the Patient Care Advocate, a non-medical person. Parents were assured that their participation was voluntary and they could withdraw their child from the study at any time without negative consequences to their infant’s medical care. Parents were given an opportunity to ask questions. Privacy, confidentiality and security of protected health information (PHI) related to this research were handled in compliance with the institution’s policies and procedures regarding Health Insurance Portability and Accountability Act regulations and mandates. All consent forms were kept separate from the raw data. Research data, coded data collection forms and records containing PHI were stored in a cabinet locked in the PI’s office, accessible to only the PI. Confidentiality was ensured by the use of a master list of code numbers corresponding with the names of the participants. The master list of linked code numbers identifying the participants was secured in a location separate from the consent forms and raw data in a password-protected file on the PI’s personal computer, in her locked office. Parents were assured that publications and presentations resulting from the study would be presented in data
aggregate form and would not identify participants by name or include other identifiers. Data will be kept on file for seven years.

Chapter Summary

This study was a randomized, investigator and parent masked placebo controlled clinical trial. A random sample of 32 infants, 16 infants per treatment group was based on a 2 x 2 repeated measures ANOVA, alpha 0.05 (two sided), standard deviation 1.2 to statistical power > .80, to detect a treatment difference (20% reduction in UWCH scores between the two interventions) with a baseline and two serial measures of pain. Each infant participated in the study at two points, the two and four month well child visit.

After receiving IRB approval, infants were included in the study if they met the inclusion criteria. Infants were excluded from study participation when they presented with conditions that would compound the effect of treatment. The experimental treatment was infants randomized to sucrose and a pacifier, the control treatment was infants randomized to sterile water and a pacifier. The University Wisconsin Children’s Hospital Pain Scale for Preverbal and Nonverbal Children measured the dependent variable, acute behavioral pain response. The scale is scored on a six point ordinal scale from zero to five; higher scores reflect a greater pain response. Cronbach’s alpha and interrater reliability is established. The scale has face, content, and constructs validity (Soetenga et al., 1999).

Data analysis utilized the intent-to-treat principle with Bonferroni adjustment for multiple comparisons. A data safety monitoring board and stopping rules monitored the safety of the infants.
CHAPTER 4
RESULTS

This chapter is divided into four sections. The first section addresses the descriptive characteristics of the study sample. The second section examines the representativeness of the study sample. The third section reports the analysis of the study research questions. The fourth and final section includes a secondary analysis that describes variables that may contribute to the variability in UWCH pain scale.

Descriptive Characteristics of Study Sample

Of the 240 infants scheduled for their newborn appointment during the recruitment period (May 2005-July 2005), 101 infants met the inclusion criteria. Infants and their parents who were not recruited for the study (n=131) either (1) were not aware of the study, (2) were not approached by the clinic nurses or (3) did not meet the inclusion criteria.

Three percent (8 of 240) of parents who wished to participate; however, could not because their infant did not meet the inclusion criteria. Two percent (4 of 240) of the infants were premature, one full-term infant was admitted to the neonatal intensive care unit with a pneumothorax, one infant was diagnosed with trisomy 21, one infant completed the two-month immunizations prior to recruitment, and language limitations prevented informed consent with one caregiver. Two parents rescheduled their infant’s two-month appointment for an earlier date, one parent canceled their two-month appointment and did not reschedule, one family moved out of state, one family’s
Participant Flow: Recruitment of Study Sample

Assessed for Eligibility (n=240)

Eligible (n=240)
Eligible, Refused (n=51)
Ineligible, Exclusion criteria (n=8)
Other (n=10)

Randomized (n=40)

Randomized to Sucrose & NNS (n=20)
Postnatal Age 6 Weeks – 2 Months (n=20)
Received allocated intervention Sucrose & NNS (n=20)
Failed to receive allocated intervention Sucrose & NNS (n=0)

Postnatal age 4 months (n=17)
Received allocated intervention Sucrose & NNS (n=17)
Fail to receive allocated intervention Sucrose & NNS
Transferred Care, Rescheduled (n=3)

Randomized to Sterile Water & NNS (n=20)
Postnatal Age 6 Weeks – 2 Months (n=20)
Received allocated intervention Sterile Water & NNS (n=20)
Failed to receive allocated intervention Sterile Water & NNS

Postnatal age 4 months (n=18)
Received allocated intervention Sterile Water & NNS (n=18)
Failed to receive allocated intervention Sterile Water & NNS
Transferred Care, Rescheduled (n=2)

Analysis
Analyzed Intent-to-treat (n=20)
telephone was disconnected, and five parents expressed an interest in the study but did not return the investigator’s telephone calls. The study was closed for enrollment July 2005 when the number of participants met the IRB approved enrollment. Figure 4.1 summarizes the participant flow through the study.

Representativeness of the Study Sample

Comparison of Infant and Maternal Characteristics

The sample for this study was recruited from Penn State Milton S. Hershey Medical Center’s Pediatric Ambulatory Clinic. To determine the sample’s generalizability to the study population, a comparison was made between the sample and data from the US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics Birth/Natality Data, and the Central Pennsylvania Center of Excellence for Research Pregnancy Outcomes at the Penn State College of Medicine (Dyer & Weisman, 2006; Hamilton et al., December 29, 2005; Martin et al., December 17, 2003, September 8, 2005; Matthews & Hamilton, June 14, 2005). Table 4.1 summarizes the infant and maternal characteristics in the study sample.

Group Comparison at Randomization

All infants approached were healthy, full-term, with a birth weight greater than 2.5 kg. The randomized groups were similar at study entry. Table 4.2 summarizes measures of central tendency and dispersion for infant variables at study entry. Table 4.3 summarizes the frequency distribution of infant variables. Table 4.4 summarizes the frequency distribution for prior painful experiences.
Declined Participation

Twenty-one percent (51 of 240) of the parents approached for the study declined participation. The most frequently cited reason was “not interested in research” (n=48). Other reasons for refusal were (1) moving into a new house (n=1), (2) husband in Iraq, research would be too stressful (n=1), and (3) infant’s grandmother did not want anyone experimenting with her grandchild (n=1).

Table 4.1 Comparison of Infant and Maternal Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sample (n=40)</th>
<th>Pennsylvania (n=Total Birth)</th>
<th>United States (n=Total Birth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singleton Pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freq (%)</td>
<td>40 (100)</td>
<td>138,039 (96.6)(^1)</td>
<td>3,953,622 (96.7)(^5)</td>
</tr>
<tr>
<td>Breast-fed for any Extent at 2-3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freq (%)</td>
<td>25 (63)</td>
<td>493 (59.2)(^2)</td>
<td>1771 (51.5)(^6)</td>
</tr>
<tr>
<td>Birth weight, mean (SD)</td>
<td>3,573 gm (74.6)</td>
<td>3,304.26 gm (620.93)(^3)</td>
<td>3,325 gm (571)(^5)</td>
</tr>
<tr>
<td>Sex Ratio, Male/Female (%)</td>
<td>22/18 (122)</td>
<td>75,575/72,315 (104)(^4)</td>
<td>2,057,979/1,963,747 (104.8)(^7)</td>
</tr>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freq (%)</td>
<td>27 (67)</td>
<td>109,761 (75.2)(^1)</td>
<td>2,917,953 (70.9)(^8)</td>
</tr>
<tr>
<td>Caesarean Delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freq (%)</td>
<td>13 (33)</td>
<td>36,198 (24.8)(^1)</td>
<td>1,197,637 (29.1)(^8)</td>
</tr>
</tbody>
</table>

Adapted from: 1 (Sutton & Matthews, 2002); 2 (Centers for Disease Control and Prevention, 2004); 3 (Dyer & Weisman, 2006); 4 (Pennsylvania Department of Health, 1996); 5 (Martin et al., September 8, 2005); 6 (Li, Darling, Maurice, Barker, & Grummer-Strawn, 2005); 7 (Matthews & Hamilton, June 14, 2005); 8 (Hamilton, Martin, Ventura, Sutton, & Menacker, December 29, 2005).
### Table 4.2 Measures of Central Tendency and Dispersion

<table>
<thead>
<tr>
<th>Infant Variable</th>
<th>Sucrose mean (SD)</th>
<th>Sterile Water mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age</td>
<td>39.65 (1.31)</td>
<td>39.4 (0.94)</td>
<td>0.4921</td>
</tr>
<tr>
<td>Birth Weight</td>
<td>3.69 (0.93)</td>
<td>3.46 (0.50)</td>
<td>0.3516</td>
</tr>
<tr>
<td>Weight at Two Months</td>
<td>5.44 (0.77)</td>
<td>5.52 (0.94)</td>
<td>0.7571</td>
</tr>
<tr>
<td>Weight at Four Months</td>
<td>6.48 (1.69)</td>
<td>7.0 (1.28)</td>
<td>0.3128</td>
</tr>
<tr>
<td>Age at Two Month Visit</td>
<td>8.68 (1.46)</td>
<td>9.2 (1.15)</td>
<td>0.2261</td>
</tr>
<tr>
<td>Age at Four Month Visit</td>
<td>17.88 (0.99)</td>
<td>18.28 (1.32)</td>
<td>0.3260</td>
</tr>
</tbody>
</table>

### Table 4.3 Frequency Distribution of Infant Variables

<table>
<thead>
<tr>
<th>Infant Characteristics</th>
<th>Sucrose &amp; NNS (n=20) Freq (%)</th>
<th>Sterile Water &amp; NNS (n=20) Freq (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (30)</td>
<td>10 (25)</td>
<td>22 (55)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (20)</td>
<td>10 (25)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Multiple birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singleton birth</td>
<td>20 (50)</td>
<td>20 (50)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast fed</td>
<td>13 (32.5)</td>
<td>12 (30)</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Bottle</td>
<td>7 (17.5)</td>
<td>8 (20)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Type of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous Vaginal</td>
<td>13 (32.5)</td>
<td>14 (35)</td>
<td>27 (67.5)</td>
</tr>
<tr>
<td>Vacuum assisted</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Forceps assisted</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Breech</td>
<td>2 (5)</td>
<td>1 (2.5)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Caesarean</td>
<td>7 (17.5)</td>
<td>6 (15)</td>
<td>13 (32.5)</td>
</tr>
</tbody>
</table>
Table 4.4 Frequency Distribution for Prior Painful Experiences

<table>
<thead>
<tr>
<th>Painful Procedure</th>
<th>Sucrose &amp; NNS (n=20) Freq (%)</th>
<th>Sterile Water &amp; NNS (n=20) Freq (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncircumcised</td>
<td>8 (20)</td>
<td>10 (25)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Circumcised</td>
<td>12 (30)</td>
<td>10 (25)</td>
<td>22 (55)</td>
</tr>
<tr>
<td>Bilirubin (heel lance)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12 (30)</td>
<td>19 (47)</td>
<td>31 (77.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>8 (20)</td>
<td>1 (2.5)</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>PKU (heel lance)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20 (50)</td>
<td>20 (50)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aqua-Mephyton (injection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20 (50)</td>
<td>20 (50)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B (injection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Yes</td>
<td>19 (47.5)</td>
<td>19 (47.5)</td>
<td>38 (95)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Meningitis</td>
<td>1</td>
<td></td>
<td>8 (20)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Reflux</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Received analgesia for prior painful procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (32.5)</td>
<td>14 (35)</td>
<td>27 (67.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (17.5)</td>
<td>6 (15)</td>
<td>13 (32.5)</td>
</tr>
</tbody>
</table>
Comparison of Study Participants and Losses to Follow-up

The number of infants lost to follow-up was small (5 of 40) and below the anticipated 20% attrition approved by the IRB. At two months of age, all randomized study participants (40 of 40) had a baseline three-minute and six-minute UWCH pain score. At four months of age, the five infants’ follow-up data were lost. During the four-month study period, a participating pediatrician relocated to a new practice site. Three infants followed the pediatrician to the new practice site. The remaining two infants rescheduled their four-month appointment for an earlier date. The PI was unaware of the rescheduled appointment. No differences between study participants and losses to follow-up were found. Table 4.5 summarizes the infant characteristics in the study sample and losses to follow-up.

Table 4.5 Comparison of Study Participants and Losses to Follow-up

<table>
<thead>
<tr>
<th>Participants</th>
<th>Infant Characteristic</th>
<th>Mean (SD)</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed Study</td>
<td>Gestational age at birth in weeks</td>
<td>39.54 (0.98)</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>(n=35)</td>
<td>Birth weight</td>
<td>3.61 (0.78)</td>
<td>2.67</td>
<td>7.23</td>
</tr>
<tr>
<td></td>
<td>Sex ratio (male/female) (%)</td>
<td>20/15 (133%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>Gestational age at birth in weeks</td>
<td>39.40 (2.07)</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>(n=5)</td>
<td>Birth weight</td>
<td>3.33 (0.43)</td>
<td>2.80</td>
<td>3.80</td>
</tr>
<tr>
<td></td>
<td>Sex ratio (male/female) (%)</td>
<td>2/3 (66%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hypothesis: Primary Research Question

The primary question of the study was to determine the analgesic properties of a 24% sucrose solution and NNS as a pre-procedural intervention for infants experiencing routine immunizations compared to a volume-equivalent sterile water solution and NNS. Analysis was intent-to-treat and involved all patients randomly assigned to the treatment and control groups.

Contrasts were constructed, combining age groups within treatment, in order to test for a difference in change in behavioral pain response between sucrose and sterile water at two minutes and five minutes following treatment administration. Bonferroni adjustment of the p-value for multiple comparisons was less than 0.01. A statistically significant difference was found between sucrose and sterile water for the change in pain response from baseline to five minutes following treatment administration. No significant difference was found for change in pain response from baseline to two minutes following treatment administration. The mean difference in UWCH pain scores between treatments following routine immunizations are summarized in Tables 4.6.

Table 4.6 Differences in UWCH Pain Scores between Treatments

<table>
<thead>
<tr>
<th>Change in Behavioral Pain Response</th>
<th>Sucrose Mean (95% CI)*</th>
<th>Sterile Water Mean (95% CI)*</th>
<th>Difference in Pain Scores Mean (95% CI)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two Minutes-Baseline</td>
<td>4.54 (4.12, 4.95)</td>
<td>4.39 (3.99, 4.80)</td>
<td>0.14 (-0.63, 0.92)</td>
<td>0.9588</td>
</tr>
<tr>
<td>Five Minutes-Baseline</td>
<td>0.27 (-0.29, 0.84)</td>
<td>3.02 (2.46, 3.58)</td>
<td>-2.74 (-3.80, -1.68)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Means and confidence intervals are model-based estimates
** Bonferroni adjusted
Figure 4.2 illustrates the change in behavioral pain response between sucrose and sterile water. There was a statistically significant difference in UWCH pain scores at five minutes following treatment administration.

Figure 4.2 Changes in Behavioral Pain Response between Sucrose and Sterile Water at Two and Five Minutes Following Treatment Administration
Hypothesis: Second Research Question

The second research question examined age-related changes in behavioral pain responses during routine immunizations after the administration of a 24% sucrose solution and NNS compared to a volume-equivalent dose of a sterile water control solution and NNS in an infant at two and four months of age. Analysis was intent-to-treat and involved all patients randomly assigned to the treatment and control groups.

Rather than analyzing behavioral pain response at zero, two and five minutes, behavioral pain response was analyzed as change in behavioral pain response from baseline to two minutes and from baseline to five minutes to account for varying baseline behavioral pain measures. Within each treatment, contrasts were constructed to test for a difference in behavioral pain response between two and four months of age at two minutes and five minutes following treatment administration. Without adjusting for multiple comparisons, none of these four contrasts were found to be statistically significant. The comparisons between the intervention group at two and four months of age following routine immunizations are summarized in Table 4.7.

Table 4.7: Comparisons of UWCH Pain Scores between Age Groups

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Change in Behavioral Pain Response</th>
<th>2 Months Mean (95% CI)*</th>
<th>4 Months Mean (95% CI)*</th>
<th>Difference 2 Months-4 Months Mean (95% CI)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose</td>
<td>Two Minutes-Baseline</td>
<td>4.5 (4.00, 5.00)</td>
<td>4.58 (3.96, 5.20)</td>
<td>-0.08 (-1.29, 1.13)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Five Minutes-Baseline</td>
<td>0.20 (-0.49, 0.89)</td>
<td>0.35 (-0.50, 1.20)</td>
<td>-0.15 (-1.80, 1.50)</td>
<td>1.000</td>
</tr>
<tr>
<td>Sterile Water</td>
<td>Two Minutes-Baseline</td>
<td>4.35 (3.85, 4.85)</td>
<td>4.44 (3.84, 5.04)</td>
<td>-0.09 (-1.28, 1.10)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Five Minutes-Baseline</td>
<td>3.25 (2.56, 3.94)</td>
<td>2.78 (1.96, 3.61)</td>
<td>0.47 (-1.15, 2.09)</td>
<td>0.9801</td>
</tr>
</tbody>
</table>

* Means and confidence intervals are model-based estimates
** Bonferroni adjusted
Figures 4.3 and 4.4 illustrate the age related change in behavioral pain response within sucrose and sterile water. There was no statistically significant difference in UWCH pain scores between at two and four months of age at two and five minutes following treatment administration.

Figure 4.3 Changes in Behavioral Pain Response between Sucrose at Two and Four Months of Age

Figure 4.4 Changes in Behavioral Pain Response between Sterile Water at Two and Four Months of Age
Comparison of Study Participants and Infants Involved in Protocol Deviations

Five infants violated the protocol by feeding immediately before the intervention, one infant in the two-month group and four infants in the four-month group. Parents stated that they felt the source of their infant’s distress was due to hunger, and that was their reason for feeding. To determine if data from infants involved in protocol deviations (n=5) contributed to variability in outcome, the data from the infants involved in protocol deviations was eliminated from analysis.

Contrasts were constructed, combining age groups within treatment, in order to test for a difference in change in pain response between the treatments of sucrose and sterile water at two minutes and five minutes following treatment administration. A statistically significant difference was found between sucrose and sterile water treatments for the change in pain response from baseline to five minutes following treatment administration. No significant difference was found for change in pain response from baseline to two minutes following treatment administration. Bonferroni adjustment of the p-value for multiple comparisons was less than 0.01. The mean difference in UWCH pain scores between treatments following routine immunizations is summarized in Tables 4.8.

Table 4.8 Comparison of Treatments-Protocol Deviations Excluded

<table>
<thead>
<tr>
<th>Change in Behavioral Pain Response</th>
<th>Sucrose Mean (95% CI)*</th>
<th>Sterile Water Mean (95% CI)*</th>
<th>Difference Sucrose-Sterile Water Mean (95% CI)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two Minutes-Baseline</td>
<td>4.52 (4.11, 4.92)</td>
<td>4.43 (3.99, 4.87)</td>
<td>0.08 (-0.71, 0.88)</td>
<td>0.9917</td>
</tr>
<tr>
<td>Five Minutes-Baseline</td>
<td>0.29 (-0.27, 0.85)</td>
<td>3.30 (2.70, 3.90)</td>
<td>-3.01 (-4.10, -1.92)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Means and confidence intervals are model-based estimates
** Bonferroni adjusted
Within each treatment, contrasts were constructed to test for a difference in change in behavioral pain response between two and four months of age at two minutes and five minutes following treatment administration. Without adjusting for multiple comparisons, none of these four contrasts were found to be statistically significant. The comparisons between intervention groups without the infants involved in protocol deviations, at two and four months of age following routine immunizations are summarized in Tables 4.9.

Table 4.9 Comparison of Intervention Groups-Protocol Deviations Excluded

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Change in Behavioral Pain Response</th>
<th>2 Months Mean (95% CI)*</th>
<th>4 Months Mean (95% CI)*</th>
<th>Difference 2 Months-4 Months Mean (95% CI)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose Two Minutes-Baseline</td>
<td>4.47 ( 3.96, 4.98)</td>
<td>4.56 ( 3.93, 5.19)</td>
<td>-0.08 (-1.35, 1.18)</td>
<td>1.0000</td>
<td></td>
</tr>
<tr>
<td>Sterile Water Two Minutes-Baseline</td>
<td>0.21 (-0.49, 0.91)</td>
<td>0.37 (-0.48, 1.23)</td>
<td>-0.16 (-1.89, 1.57)</td>
<td>1.0000</td>
<td></td>
</tr>
<tr>
<td>Sterile Water Five Minutes-Baseline</td>
<td>4.44 ( 3.88, 4.99)</td>
<td>4.43 ( 3.76, 5.10)</td>
<td>0.01 (-1.35, 1.38)</td>
<td>1.0000</td>
<td></td>
</tr>
<tr>
<td>Sterile Water Five Minutes-Baseline</td>
<td>3.31 ( 2.55, 4.07)</td>
<td>3.29 ( 2.37, 4.20)</td>
<td>0.03 (-1.84, 1.89)</td>
<td>1.0000</td>
<td></td>
</tr>
</tbody>
</table>

* Means and confidence intervals are model-based estimates
** Bonferroni adjusted
Adverse Events

Combining the two- and four-month age groups, 13% of the infants (5 of 40) experienced an adverse event during the administration of a study solution. Within the five events, three occurred in the two-month groups and two occurred in the four-month group. In the two-month group, two infants randomized to the sucrose group coughed and one infant randomized to the sterile water group gagged. Within the four-month group, two infants randomized to the sucrose group coughed. No infants in the four-month group randomized to the sterile water group experienced an adverse event. All infants recovered spontaneously within ten seconds. None of the events were considered clinically significant by the attending pediatrician or the study’s data safety monitoring board.

Stopping rules were not employed and no interim analysis was performed. Table 4.10 summarized the frequency of adverse events and the infants’ behavioral states prior to the adverse event.

Table 4.10: Frequency of Study Adverse Events

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Two Months of Age (n=3) Freq (%)</th>
<th>Infant Behavioral State Prior to Administration of Solution</th>
<th>Four Months of Age (n=2) Freq (%)</th>
<th>Infant Behavioral State Prior to Administration of Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose</td>
<td>Cough 2 (5)</td>
<td>Calm, relaxed (n=1)</td>
<td>2 (5)</td>
<td>Calm, relaxed (n=1)</td>
</tr>
<tr>
<td></td>
<td>Crying, Inconsol (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile Water</td>
<td>Gagged 1 (3)</td>
<td>Calm, relaxed (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prior Painful Experiences

Male circumcision was the paradigm utilized to determine if prior analgesia for painful experiences would contribute to a decrease in behavioral pain response scores in infants at their two- and four-month well-child appointment. Within each treatment, contrasts were constructed to establish means in behavioral pain response between condition (received analgesia for prior painful experience, did not receive analgesia for prior painful experience) at two minutes and five minutes following administration for two and four months of age. Intent-to-treat analysis included missing data of two male infants at four months of age. The comparisons between analgesia conditions and treatments at two and four months of age following routine immunizations are summarized in Table 4.11.

Table 4.11 Comparisons between Analgesia Conditions and Treatments

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Change in Behavioral Pain Response</th>
<th>No Prior Analgesia Mean (95% CI)</th>
<th>Prior Analgesia Mean 95% CI</th>
<th>Diff Analgesia - No Analgesia 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose</td>
<td>Two Mon</td>
<td>Two Min-Baseline</td>
<td>4.8 (4.24, 5.36)</td>
<td>5 (5, 5)</td>
<td>-0.2 (-0.36, 0.76)</td>
<td>0.374</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Five Min-Baseline</td>
<td>0.2 (-0.36, 0.76)</td>
<td>0.714 (-0.17, 1.59)</td>
<td>-0.514 (-1.54, 0.52)</td>
<td>0.291</td>
</tr>
<tr>
<td>Sterile Water</td>
<td>Four Mon</td>
<td>Two Min-Baseline</td>
<td>4.6 (3.49, 5.71)</td>
<td>5 (5, 5)</td>
<td>-0.4 (-1.14, 0.34)</td>
<td>0.255</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Five Min-Baseline</td>
<td>0.2 (-0.36, 0.76)</td>
<td>1 (-0.19, 2.19)</td>
<td>-0.8 (-2.16, 0.56)</td>
<td>0.218</td>
</tr>
<tr>
<td></td>
<td>Two Mon</td>
<td>Two Min-Baseline</td>
<td>5 (5, 5)</td>
<td>5 (5, 5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Five Min-Baseline</td>
<td>4.5 (2.91, 6.09)</td>
<td>3.17 (1.24, 5.09)</td>
<td>1.33 (-1.01, 3.68)</td>
<td>0.373</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two Min-Baseline</td>
<td>5 (5, 5)</td>
<td>4.8 (4.24, 5.36)</td>
<td>0.2 (-0.45, 0.85)</td>
<td>0.226</td>
</tr>
<tr>
<td></td>
<td>Four Mon</td>
<td>5 Min-Baseline</td>
<td>2.67 (-3.59, 8.92)</td>
<td>3.6 (0.88, 6.32)</td>
<td>-0.93 (-5.05, 3.18)</td>
<td>0.599</td>
</tr>
</tbody>
</table>
Figures 4.5 and 4.6 illustrate the comparison of behavioral pain response within analgesic conditions at two and four months of age.

Figure 4.5 Comparisons of Behavioral Pain Response Scores within Analgesia Condition at Two Months of Age

![Graph showing comparisons of behavioral pain response scores at two months of age](image)

Figure 4.6 Comparisons of Mean Behavioral Pain Response Scores within Analgesia Condition at Four Months of Age

![Graph showing comparisons of mean behavioral pain response scores at four months of age](image)
Secondary Analysis

A model building process using regression analysis was utilized to determine the effect of gender, nutrition (whether or not the infant was breast fed), number of prior painful experiences and analgesia (whether or not the infant received analgesia for a prior painful experience) on behavioral pain response as measured by UWCH pain scale.

Four separate models were created. Each model contained the three main effects from the primary analysis, treatment, time, and age group, as well as the significant interaction, treatment by time. Each variable, gender, nutrition, number of prior painful experiences and analgesia was added to the model independently to assess its contribution. Gender (p = 0.1865), nutrition (p = 0.8096), number of prior painful experiences (p = 0.2159), and analgesia (p = 0.2266) were all found to be statistically nonsignificant.

Summary of Results

While there was no statistically significant differences in UWCH pain scores within sucrose and sterile water, an infant at two and four months of age at two and five minutes following treatment administration, there was a significant reduction in UWCH pain scores in the sucrose and NNS group at baseline to five minutes compared to the sterile water and NNS group. Pain was measured utilizing a valid, composite, multivariable pain scale, the UWCH Pain Scale (Soetenga et al., 1999).

The data suggest, following three serial immunizations, that changes in behavioral pain response in the sucrose and NNS group were not statistically significantly from the
sterile water and NNS group at two and four months of age at two minutes following treatment administration (p-value=1.00).

Change in pain response from baseline to two minutes following sucrose and NNS or sterile water and NNS administration was not statistically significant (p-value=0.958). Between treatments, however, sucrose and NNS reduced behavior pain response in infants at two and four months of age at baseline to five minutes (p<0.0001). The effect of gender (p=0.1865), nutrition (p=0.8096), prior painful experiences (p=0.2159), and analgesia (p=0.2266) on behavioral pain response were statistically nonsignificant.

The number of infants lost to follow-up was 13% (5 of 40) which is below the anticipated 20% attrition approved by the IRB. Thirteen percent (5 of 40) of the infants were involved in protocol deviations. Analysis excluding their data did not underestimate the findings of the study. Very few adverse events (5 of 40) occurred during the study. Each adverse event self-resolved within ten seconds. Stopping rules were not employed. Table 4.12 summarizes the research results.

Table 4.12: Summary of Research Results

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Statistical Value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference in mean (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Effectiveness of Oral Sucrose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two Minutes to Baseline</td>
<td>0.14 (-0.63, 0.92)</td>
<td>0.9588</td>
</tr>
<tr>
<td>Five Minutes to Baseline</td>
<td>-2.74 (-3.80, -1.68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age Related Changes in Effectiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two Months - Four Months of Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two Minutes to Baseline</td>
<td>-0.08 (-1.29, 1.13)</td>
<td>1.000</td>
</tr>
<tr>
<td>Five Minutes to Baseline</td>
<td>-0.15 (-1.80, 1.50)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
CHAPTER 5

DISCUSSION

The purpose of this randomized clinical trial was to investigate the analgesic properties of intraoral sucrose on repeated painful procedures (three serial routine immunizations) in an infant at two and four months of age. A secondary purpose was to investigate the age-related changes in analgesia within an infant between two and four months of age. Findings from this study will advance the knowledge in pediatric procedural pain management and provide strong evidence for the development of evidence-based guidelines for practice and research.

This chapter is divided into five sections. In the first section, a synopsis of key findings and explanations is offered. The second section positions this study within the current literature. The third section considers the strengths and limitation of the study. The fourth section offers clinical and research implications of the work. The fifth and final section, a conclusion, presents a position for future initiatives.

Key Findings and Explanations

The results of this research support the hypothesis and provide preliminary evidence of the clinical efficacy and safety of sucrose in infants at two and four months of age. That is, there is a significant difference in the sucrose and NNS intervention group compared to the sterile water group at baseline to five minutes. This study promotes the implementation of glycomic interventions to provide comfort for infants during routine immunizations.
Hypothesis: Primary Research Question

The primary question of the study was to determine the analgesic properties of a 24% sucrose solution and NNS as a pre-procedural intervention for infants experiencing routine immunizations compared to a volume-equivalent sterile water solution and NNS. When age groups were combined within treatments, sucrose and NNS was not effective for decreasing behavioral pain response at two minutes following solution administration. At two minutes after solution administration, infants who received sucrose prior to immunizations (n=20) had a mean behavioral response pain score of 4.45 (95% CI 4.12, 4.95) compared to infants who received sterile water prior to routine immunizations (n=20) 4.39 (95% CI 3.99, 0.92). The difference between the mean behavioral pain response score from baseline to two minutes at two and four months of age was 0.14 (95% CI -0.63, 0.92), suggesting that there is no significant difference between sucrose and sterile water during routine immunizations two minutes after solution administration (p=0.9588). Although childhood vaccines are generally regarded as a benign procedure, this research supports an earlier study suggesting a substantial portion of infants experience significant levels of pain and distress with routine immunizations (Jacobson et al., 2001).

There was a significant difference in behavioral response scores between the sucrose and sterile water groups at baseline to five minutes. In both age groups, two and four months of age, the behavioral pain response scores were significantly higher in sterile water group compared to sucrose group five minutes after routine immunization. At five minutes after solution administration, the same infants who received sucrose prior to routine immunizations had a mean behavioral response pain score of 0.27 (95% CI -
0.29, 0.84) compared to infants who received sterile water prior to immunizations 3.02 (95% CI 2.46, 3.58). The difference between the means was -2.74 (95% CI -3.80, -1.68), suggesting that at two and four months of age, there is significant difference between sucrose and sterile water during routine immunizations five minutes after solution administration (p<0.0001). The increased behavioral response scores in the sterile water group suggest greater pain intensity among the infants receiving sterile water compared to infants in the sucrose group. This data suggest that oral sucrose and NNS administered as a pre-procedural analgesic prior to routine immunizations decreased behavioral pain response for infants at two and four months of age at baseline to five minutes as measured with a validated multivariate behavioral pain scale (Soetenga et al., 1999).

The evidence suggests that a 24% intraoral sucrose solution, 0.6 ml/kg (0.3ml/lb) and NNS may not be effective in balancing the pain intensity or decreasing behavioral pain response during the injection phase of the routine immunization procedure, but may be adequate for mitigating the behavioral pain response and distress that infants experience following immunizations. Further research should be conducted to determine if immunization pain can be mitigated with alterations in dose, concentration, or the delivery method of sucrose.

**Hypothesis Second Research Question**

The secondary research question examined age-related changes in behavioral pain responses in an infant during routine immunizations at two and four months of age after the administration of a 24% sucrose solution compared to a sterile water control solution. Since baseline behavioral pain response scores varied with individual infants, analyzing
behavioral pain response at baseline, two and five minutes would not represent an accurate change in behavioral response. Therefore, within each age group, contrasts were constructed to test for a difference in behavioral pain response at two minutes and five minutes following treatment administration. The following discussion will examine age-related changes within treatment groups.

**Sucrose**

The mean behavioral pain response for two-month infants at two minutes after solution administration was 4.5 (95% CI 4.00, 5.00), compared to the mean behavioral pain response for four-month infants at two minutes after solution administration which was 4.58 (95% CI 3.96, 5.20). The difference in these two means, -0.08 (95% CI -1.29, 1.13), is not statistically significant (p-value=1.000).

This finding did not differ from the behavioral pain responses at five minutes in the two- and four-month age group. The mean behavioral pain response for two-month infants at five minutes after solution administration was 0.2 (95% CI -0.49, 0.89) compared to the mean behavioral pain response for the infant at four-month infants at five minutes after solution administration 0.35 (95% CI -0.50, 1.20). The difference in the two- and four-month behavioral pain response means, -0.15 (95% CI -1.80, 1.50) does not represent a statistically significant difference (p-value=1.000). These findings suggest that in the infants who received sucrose, there was not a statistically significant difference in the behavioral pain response in the sucrose group at two and four months of age, suggesting that the analgesic properties of sucrose may be equivalent in both age groups. Of interest is the observation that the difference in mean behavioral pain response scores is slightly higher in the four-month group compared to the two-month group. Although
insignificant, this observation may suggest there is a diminishing effect of sucrose with increasing age. Further research is necessary to establish the point at which sucrose is no longer effective in diminishing mild to moderate pain.

**Sterile Water**

There were similar nonsignificant findings when behavioral pain response scores were compared in the sterile water group at two minutes for infants at two and four months of age. The mean behavioral pain response for infants at two-months at two minutes after sterile water administration was 4.35 (95% CI 3.85, 4.85) compared to the mean behavioral pain response for the same infants at four-month infants at two minutes after solution administration which was 4.44 (95% CI 3.84, 5.04). The difference in these two means, -0.09 (95% CI -1.28, 1.10), is not statistically significant (p-value=1.000).

The mean behavioral pain response for infants at two-months at five minutes after sterile water administration was 3.25 (95% CI 2.56, 3.94) compared to the mean behavioral pain response for the same infants at four-month at five minutes after solution administration 2.78 (95% CI 1.96, 3.61). The difference in the two- and four-month behavioral pain response means, 0.47 (95% CI -1.15, 2.09), does not represent a statistically significant difference (p-value=0.9801). Although the differences are statistically insignificant, the sterile water two-month group displayed higher pain scores than the sterile water four-month group at five minutes after routine immunizations. One possible explanation may be the increased pain sensitivity due to the immaturity of pain-modulating mechanism in the two-month age group (Anand et al., 1999; Andrews & Fitzgerald, 1994; Coskun & Anand, 2000; Craig & Grunau, 1993; Fitzgerald, 1985, 2000; Johnston et al., 1996; Walden et al., 2001).
Secondary Analysis

In this study, UWCH pain scores were significantly associated with the three main effects from the primary analysis, treatment, time, and age group, as well as the significant interaction, treatment by time. The hypothesis that sucrose and NNS would decrease behavioral pain response during routine immunization was supported within the two- and four-month age group.

The model building process using regression analysis created four separate models. Each independent model contained the main effects from the primary analysis, treatment, time, and age group, as well as the significant interaction, treatment by time. Gender (p = 0.1865); nutrition, whether or not infant was breast fed (p = 0.8096); number of prior painful experiences (p = 0.2159) and analgesia, whether the infant received analgesia for a prior painful experience (p = 0.2266) were all found to be statistically nonsignificant.

Breast feeding was an insignificant variable in the model. Although studies have documented the analgesic properties of breast feeding (Gray, Miller, Philipp, & Blass, 2002), in the present study, no statistically significant relationship was found between breast feeding and a composite multivariable behavioral pain response. Further research is required to determine the analgesic effects of breast feeding and its contribution to decreasing behavioral pain response to the state organization properties of breast feeding.

When mean behavioral response scores of infants involved in feeding protocol deviations were omitted from data analysis, there was no significant variability in the mean difference of two- and four-month behavioral pain response scores at two and five minutes after solution administration in all four constructs; (1) Sucrose at two minutes
(p=1.000), (2) Sucrose at five minutes (p=1.000), 31) Sterile water at two minutes (p=1.000), and (2) Sterile water at five minutes (p=1.000). It is not unexpected to find that lactose does not significantly influence behavioral pain response scores since previous studies have demonstrated lactose’s ineffectiveness in decreasing behavioral pain response scores (Blass & Shide, 1994; Blass & Smith, 1992).

Although the sex ratio (males/females) was higher in the sucrose group 12/8 (150%), compared to the sterile water group, 10/10 (100%), there was no statistically significant difference in mean behavioral response scores in the two- and four-month age group at five minutes after solution administration (p-value = 0.3232). Previous studies examining the effects of gender on newborn pain response have nonsignificant results (Fuller, 2002; Ipp et al., 2004).

Two previous studies have been done to determine the duration and intensity of infant cry after immunizations administered months after newborn circumcisions were done without analgesia (Taddio et al., 1995; Taddio et al., 1997). This research extends those studies. Although the difference was nonsignificant (p=0.373), analysis of data from the study found that infants in the two-month sterile water group who received analgesia prior to their circumcisions, had lower behavioral pain response scores at baseline to five minutes (3.17 [1.24, 5.09]) than infants who did not receive analgesia prior to their circumcision (4.5 [2.91, 6.09]). Although the findings are nonsignificant, infants in the remaining groups who received analgesia prior to their circumcisions displayed higher behavioral pain response scores than infants who did not receive analgesia prior to circumcision. The conceptualization of pain in the earlier studies may have contributed to the variability in outcomes. The previous studies outcome measures
for pain were cry duration and intensity. These outcomes do not accurately represent infant pain (Stevens, Yamada, & Ohlsson, 2001a). Infant cry duration in previous studies may have been a better representation of infant distress instead of infant pain. The proposed conceptualization of pain is congruent with a multidimensional definition of pain which accurately represents an infant’s behavioral pain response (Stevens et al., 2001a; Stevens & Ohlsson, 1998; Stevens, Yamada et al., 2004) Further research in this area is required to determine the contribution of preemptive analgesia for mitigating the effects of noxious stimuli on the developing nervous system.

The variables birth weight and gestational age were collected but not included in the model. The American Academy of Pediatrics, Committee on Fetus and Newborn, recognizes the birth weight/gestational age relationship in predicting neonatal morbidity and mortality and recommends all newborns be classified in this fashion (American Academy of Pediatrics & American College of Obstetricians and Gynecologists, 2002; Pittard, 1993). Morbidity and mortality, birth weight, and gestational age were utilized as inclusion criteria because of their significance in predicting neonatal maturity.

The primary outcome of this study was not to predict infant pain. Identifying infant characteristics that contribute to the variability of behavioral pain response is important for establishing criteria to define pediatric pain management. Larger studies constructed with a more heterogeneous sample of infants will be required to examine variables account for the variability in behavioral pain response.

Comparison with Relevant Findings from Other Published Studies

This study provides a unique contribution to the efficacy of sucrose in postnatal infants. Previous studies failed to provide a conceptual definition of pain or scientific
rationale for how pain was linked to the outcomes of interest. Further limitations of the studies were small heterogeneous samples; variable doses, concentrations and delivery methods of sucrose; and the noxious stimulus was not a painful event. The current research utilizes a composite pain assessment, an established dose, a controlled concentration and delivery method of sucrose, and provides an accurate representation of a painful event. This section will contrast findings from this study with the results of previous studies. Methodological strengths and limitations will be discussed in the next section.

In previous studies (Allen et al., 1996; Barr et al., 1995; Lewindon et al., 1998; Ramenghi et al., 2002; Reis et al., 2003), the outcome of interest was the proportion, percentage, or duration of cry. No scientific rationale linking cry to infant pain was offered in any of the studies. This study used composite pain assessment and multidimensional approach to pain measurement that represents a more comprehensive conceptualization of pain (Stevens et al., 2001a; Stevens & Ohlsson, 1998; Stevens, Yamada et al., 2004). Compared to the descriptive statistics of previous studies, moreover, this study’s data analysis provided a more robust analysis of the data through a repeated measures ANOVA, a model examining characteristics than may influence variability in the outcome, and secondary analysis of key variables. Finding from this study established the existence of pain in infants within age and time and quantified pain intensity in infants during routine immunizations. The validity and reliability of the instrument provided strong evidence for clinical practice decision-making.

Dose, concentration, and delivery method of sucrose varied in previous studies (Allen et al., 1996; Barr et al., 1995; Lewindon et al., 1998; Ramenghi et al., 2002; Reis
et al., 2003). Doses ranged from 2mls delivered by pipette to 10ml administered in an infant’s bottle. Sucrose concentrations ranged from 12% to 75% (Allen et al., 1996; Barr et al., 1995; Lewindon et al., 1998; Ramenghi et al., 2002; Reis et al., 2003). The established dose of sucrose, 2ml of a 24% solution administered two minutes prior to a painful experiences, is documented in serial Cochrane Collaborative systematic reviews (Stevens et al., 2001a; Stevens & Ohlsson, 1998; Stevens, Yamada et al., 2004). This study utilized the established sucrose dose for term infants from Cochrane year insert and adjusted the volume according to the infant’s weight; therefore, unlike previous studies, all infants in the study received the same amount of solution calculated at weight/volume. This controlled measure of solution prevented bias resulting from the variability of dose and concentration and established the effectiveness of the sucrose analgesia in infants within age group and time.

Another limitation of the previous studies was the variability in the representation of the noxious stimulus. In earlier studies (Allen et al., 1996; Barr et al., 1995; Lewindon et al., 1998; Ramenghi et al., 2002; Reis et al., 2003), the number of injections varied from one to four injections during the immunization procedure. Infants routinely receive multiple injections during their visit. Clinic nurses in this study administered the same immunizations in the order described in the study protocol to each child in the study. The technique conformed to national standards for immunization administration (American Academy of Pediatrics, 2003). Compliance with protocol guidelines minimized bias and strengthened interval validity within the study. By administering the immunizations following the Department of Health, Center for Disease Control’s guidelines (American
Academy of Pediatrics Committee on Infectious Diseases, 2006) the study was positioned to examine the analgesic effects of sucrose in the infant’s pain paradigm.

The previous studies (Allen et al., 1996; Barr et al., 1995; Lewindon et al., 1998; Ramenghi et al., 2002; Reis et al., 2003) provided rules for exclusion of participants from data analysis. The methodology of intent-to-treat utilized in this study had the potential to underestimate the effects of treatment; however, infants involved in protocol deviations were small and did not influence the variability in behavioral pain response score within age and time. Incorporating all infants in the final analysis provides an accurate estimation of the treatment effect within the population (Guyatt et al., 2002).

This randomized, investigator-blind, placebo-controlled clinical trial investigated the analgesic properties of an oral sucrose solution in infants receiving routine immunizations at two and four months of age. Serial measures of validated behavioral pain responses were documented at each visit. Unlike earlier immunization studies of infants this age, this collaborative translational research is innovative, in that it used a composite, validated measure of pain; it had a controlled method of delivery of oral sucrose or sterile water, and controlled for the effect of dose and parental soothing on behavioral pain response during the immunizations. While previous studies examined a single painful injection, this study suggested that a weight/volume dose of 0.6ml/kg of a 24 gram/1000 ml (24%) sucrose solution would be effective in decreasing the pain intensity of three serial routine immunizations at two and four months of age. Results of the study found a combination of sucrose and NNS was effective in decreasing procedural pain during routine immunizations in infants at two and four months of age at baseline to five minutes.
Strength and Limitations

Methodological consideration must be considered when evaluating the strength of the evidence in this study. Strengths and limitations of the study design, participants, measurement and external validity will be offered for evaluation.

Design

A major strength of this study was the randomized control trial design (RCT). The RCT was the most appropriate design for establishing the effectiveness of sucrose at two and four months and for determining the age-related changes in analgesia. This collaborative translational research is innovative in that it uses a valid composite measure of pain, a controlled method of delivery of oral sucrose or sterile water, and controls for the effect of dose and parental soothing on behavioral pain response during the immunizations. The design provided well-defined recruitment, randomization and data management and analysis methods. Utilizing a standardized immunization procedure, the RCT provided a low attrition and data entry error rate. The characteristics of the participants, randomization, and measurement of the dependent variable were all controlled to eliminate bias. All infant data were analyzed using the principle of intent-to-treat. Data were considered missing only if the infant was absent from the well-child appointment. Internal validity was further strengthened by having a single investigator perform the standardized the immunization procedure.

Further development of behavioral pain response documentation during the recovery period would extend knowledge acquired from this study. Recovery behavioral pain response scores were document at five minutes after the administration of the solution. Some infants were calm and relaxed approximately thirty seconds after the final
immunization injection. Other infants did not require the full three minutes to return to baseline scores. Future studies utilizing time to event for data analysis would establish a more robust description of infant pain and distress after the administration of oral sucrose.

Participants

Participants were recruited from all eligible healthy full-term infants. A reasonably homogenous group of infants was obtained by clearly and narrowly defining the inclusion and exclusion criteria. Recruited parents were very interested and supportive of the study. Several parents asked if their infant could continue receiving the randomized solution for future immunizations. Parents whose infants were receiving care from other clinics called the investigator and asked if they could participate in the study if they were willing to transfer their infant’s care to the study site. After the study was closed to recruitment, twenty-eight parents called the investigator wanting to enroll their infant in the study.

One parent called to inquire about recruitment of her preterm infant into the study. Further studies comparing the analgesic effects of sucrose during routine immunization in term and preterm infant’s should be conducted.

Randomization

At randomization the intervention groups were comparable in terms of gestational age, birth weight, and age (in weeks) at enrollment. Central randomization was determined using a computer-generated randomization list created by a statistician in the Health Evaluation Science Department who was not involved in recruitment or data collection procedures. To ensure a balance over time of infants randomized to non-
nutritive sucking and sterile water with those infants randomized to non-nutritive sucking and sucrose, the computer also generated a randomization list randomizing infants in permuted blocks of four.

All infants received one of the two interventions as defined by the group to which they are randomized. The study groups were independent of each because the same infants were assessed at 2 and 4 months and the infants randomized to receive sucrose (or sterile water) at two months received sucrose (or sterile water) at four months. Parent and investigator masking was possible for both treatment groups.

Stratification for gestational age was used to control for the effects of central nervous system maturity. Although other variables influence UWCH behavioral pain response scores, sufficient knowledge of infant pain response based on neuroanatomy provided a biological rationale for stratification of age groups to control for variation in infant behavioral pain response.

Sample Size

An adequately powered sample size provided methodological rigor to the study. Existing studies examining the effectiveness of oral sucrose in infants included small sample sizes that were unable to detect significant differences in behavioral pain response. A sample size of thirty infants (fifteen infants per treatment group) was required to detect a treatment difference with an alpha at 0.05 (two-sided), statistical power 0.80. The randomized sample was stratified and equally divided among the two treatment and age groups. Forty infants were recruited to account for participant attrition, disenrollment or misplaced data. The adjusted sample size provided twenty infants per treatment group.
Site

The study was carried out in a single outpatient pediatric clinic. No manipulation of the environment occurred. The use of a single research site insured tighter control of the potential sources of bias (i.e., site differences, clinic staff effect). Procedures for appointment visits (weight, length, head circumference) were standard and performed by clinic staff. The pediatric outpatient clinic immunization procedure conformed to national standards (American Academy of Pediatrics, 2003)

Measurement

Previous studies involving healthy and stable postnatal infants had conceptual and methodological limitations. The absence of a conceptual definition of pain or a scientific rationale linking pain to the outcomes of interest compromised earlier studies. The investigator’s outcome measures of proportion, percentage, or duration of crying were not valid indicators of pain in infants.

The gold standard for pain assessment and measurement is self-report. Preverbal infants are incapable of self-report therefore their pain is inferred from valid behavioral pain responses (Anand & Craig, 1996). The UWCH pain scale is a validated measure of pain for preverbal and nonverbal children. Reliability and validity of the UWCH pain scale has been established for procedural pain in this age group (Soetenga et al., 1999).

The presence of pacifiers did not prevent documentation of facial expression; pacifiers fell out of the infants’ mouths with the first injection. Thus, the ability of the infant to express a full range of facial expressions was not diminished by sucking on the pacifier. Behavioral pain response scores were not decreased.
**External Validity**

The study has good external validity. Infant characteristics from the study are comparable to the natality statistics from Pennsylvania and the United States. All infants participating in the study were delivered from a singleton pregnancy. The percentage of single births in Pennsylvania is 96.6% (Sutton & Matthews, 2002) and is comparable to the 96.7% single births in the United States (Martin et al., December 17, 2003). Sixty-three percent of the mothers in the study breast fed their infants. Fifty-nine per cent of all mothers in Pennsylvania breast feed (Centers for Disease Control and Prevention, 2004), 51.5% of mothers in the United States breast feed (Li et al., 2005). The mean birth weight in the study was 3573 grams. Pennsylvania’s mean birth weight statistic is 3304.26 grams (Dyer & Weisman, 2006), and the United States’ mean birth weight statistic, 3325 grams (Martin et al., September 8, 2005). The sex ratio in the study was slightly higher than the state and national average 22/18 (122%). State percent of males to females is 104% (Pennsylvania Department of Health, 1996) while the national percentage is 104.8 (Matthews & Hamilton, June 14, 2005). The characteristics of the study infants are closely aligned with the state and national average.

**Clinical and Research Implications**

**Clinical Implications**

Knowledge of pain prevention interventions has not been consistently translated into a decrease in prevalence or intensity of painful experiences in children. This study addresses several principles present in this study that will aid clinicians in critical evaluation of the data.
Data from this evidence-based, level II, RCT supports the utilization of sucrose as a pre-procedural intervention for the treatment of mild to moderate procedural pain. Numbers needed to treat (NNT) is the number of patients who must receive the treatment intervention over specific time to produce one positive outcome. The clinical implications of this concept provides the clinician with information to determine if the probable treatment benefits are worth the effort the healthcare provider and patient must contribute to achieve the desired outcome (Guyatt et al., 2002). At two months of age, the numbers needed to treat with sucrose in order to see a pain score of zero or one at two or five minutes is one (\(NNT = 1/(0.85 - 0.10) = 1.33\)). At four months of age, the numbers needed to treat with sucrose in order to see a pain score of zero or one at two or five minutes is two (\(NNT = 1/(0.76 - 0.22) = 1.85\)). NNT of one is a favorable value for determining if the benefits of sucrose are worth the potential harm and cost. Even though the NNT increases to two at four months, the treatment benefits of sucrose still exceed the potential harm and cost. The increase in NNT between two and four months is of interest, as it may provide another indicator of sucrose’s decreasing effectiveness with advancing age.

The ability to identify problems is a necessary skill for all evidence-based practice (EBP) clinicians in situations where choices should be driven by evidence compared to choices driven solely by personal or patient’s preference. Central figures from the Evidence-Based Practice (EBP) Group have argued that evidence (probabilities) alone is insufficient for decision making, at least in some cases, and that values and preferences (utilities) have to be considered (Sackett, Strauss, Richardson, Rosenberg, & Haynes, 2000). Like EBP, medical decision analysis requires health care providers to make
decisions about patient care. Evidence-based practice is in constant dialogue with rigorous medical decision analysis to provide a formal structure for integrating the evidence about the beneficial and harmful effects of treatment options with the values or preferences associated with those beneficial and harmful effects (Guyatt et al., 2002). This study provides the evidence to establish probabilities for a successful analgesic outcome utilizing sucrose as a pre-procedural intervention during routine immunizations in infants at two and four months of age. Qualitative and quantitative studies to establish parental utilities exist in the literature (Franck, Allen, Cox, & Winter, 2005; Gale, Franck, Kools, & Lynch, 2004; Stevens, Mcgrath et al., 2004) to help clinicians compare the expected outcomes of pursuing different treatments.

Sucrose and NNS are commercially available, inexpensive, easily administered and safe. The rapid onset and short duration of analgesia facilitate its utilization in hospitals and clinics. Although sucrose is not effective for moderate to severe pain, future research may establish its effectiveness as an adjunct treatment with other pharmacological interventions.

The current work has established the efficacy of sucrose as a pre-procedural analgesic during routine immunizations at two and four months of age at five minutes after solution administration. The established dose of sucrose utilized in the protocol did not decrease behavioral pain response scores at two minutes after solution administration at two and four months of age. The data provide an opportunity to explore the question: given the evidence that, for a single injection, sucrose is effective for a decreasing behavioral pain response scores in infants at two and four months of age, is the intensity of pain infants experience during three serial routine immunizations not balanced by this
dose or concentration of sucrose? Further research is required to determine whether sucrose influences behavioral pain response scores during the injection phase of immunizations or is responsible for decreasing the behavioral pain response following injections.

*Research Implications*

The goal of this study was to determine the effectiveness of oral sucrose during routine immunizations at two and four months of age and to determine age-related changes in analgesia over time. No attempt was made to determine if the mechanism of NNS provided additive or synergic benefits for the infant. Other studies may address this issue with pain management strategies that ethically provide some form of pain relief to balance the removal of NNS. In particular, the examination of sucrose and NNS, sterile water with NNS and sterile water with cuddling may provide insight into the combined effects of sucrose and NNS. There is sufficient pre-clinical data on sucrose to draw parallels to human infants, but the mechanisms underlying cuddling and kangaroo care in postnatal infants and young children are not as clearly documented. One explanation may be that similar to preterm infants, cuddling and calming in postnatal infants is facilitated by infant state organization.

The focus of most studies to date is the efficacy of sucrose within the paradigm of heel lance. Continued research investigating the utilization of sucrose for other painful procedures will establish its analgesic effectiveness in a diverse clinical environment. The long history of sweet solutions for calming and analgesia further increases its likelihood of acceptance of sucrose outside the medical community.
Conclusion

In the developed world, immunizations constitute a necessary frequently-occurring preventive health measure in pediatric clinics and are the most common painful intervention performed on infants. The increasing number of immunogenic vaccines has resulted in pain and distress that may decrease parental compliance and intensify the anti-vaccine sentiment. Although pain during heel lancing and venipuncture has received considerable attention, immunization injections occur far more frequently. Pain management during injections has implications for a far wider population of infants independent of race, religion socioeconomic status, or gender.

Procedure-related pain experienced during diagnostic and routine health care maintenance in the first few months of life remains inadequately managed because of the perceived relatively short-term nature of the pain. Although adults are expected to tolerate mild-to-moderate painful interventions as part of their medical care, young children are generally unable to balance current or anticipated pain against the future benefit of medical treatment. Because they lack the ability to communicate the source and severity of their pain, infants are often given minimal or no analgesia for procedures that would routinely be treated aggressively in adults.

Traditional teaching suggested that children do not experience as much pain as adults because their nervous system is not fully developed and most children have no memory of their early years (Sandkuhler, 2000). Recent animal and human studies have shown that the opposite is true. These studies propose that, due to a more robust inflammatory response and the lack of a central inhibitory influence, infants and young children experience more pain than adults. Multiple lines of evidence acknowledge
frequent or severe pain in infants as a potentially causative factor for adverse
neurodevelopmental outcomes of a more enduring nature persisting into adolescence and
adulthood (Alvares et al., 2000). The following have all been documented in school-age
children: alterations in sleep-wake cycles, lowered pain tolerance for months or years
following the procedure, impairment in learning, memory and behavior, and increased
experiences and complaints of physical distress that cannot be fully explained by a
medical diagnosis (Grunau, Whitfield et al., 1994a; Grunau, Whitfield, Petrie et al., 1994;
Porter et al., 1999).

Given the plasticity of central nervous system processing in infants, repetitive or
severe pain in infancy may produce widespread alterations in the immature brain leading
to abnormal behaviors in adulthood. Recent studies by investigators suggest that although
painful memories in infancy cannot be consciously recalled, they may be encoded in
central nervous system procedural memory and lead to abnormal behavior patterns or
altered sensory processing, perhaps for the entire life of the individual (Anand & Scalzo,
2000; Ruda et al., 2000). These findings should focus the attention of researchers and
clinicians on the long-term impact of early painful experiences and highlight the need for
translational research to develop therapeutic strategies for the management of infant pain.

The public health and economic importance of preventing or ameliorating the
subtle brain alteration and increased pain sensitivity caused by infant pain cannot be
overestimated. Concerted efforts to investigate the mechanism underlying early neuronal
activity, to minimize the impact of adverse experiences and environmental factors in
newborns, and to develop novel therapeutic strategies for improving the cognitive and
behavioral outcomes of infants require no further justification. If current theories in
glycomic research are applied to clinical practice, future generations may not have to pay the price for medical procedures performed today.

Healthy young infants have limited therapeutic alternatives for immunization pain. The direction of pain management research for infants and young children should identify a reasonable means of mitigating procedural pain. A short-acting analgesic will remove parental perception of pain as a barrier to immunization, improve compliance, and further the public health mandate that all infants be immunized. The administration of sucrose is a simple, cost-effective, evidence-based intervention to implement in outpatient pediatric clinics. Sucrose analgesia offers parents the opportunity to be advocates for the comfort for their infant and provides health care professionals with a means of alleviating pain in young children.
REFERENCES


APPENDIX A:

UNIVERSITY OF WISCONSIN CHILDREN’S HOSPITAL PAIN SCALE
<table>
<thead>
<tr>
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<th>0</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td><strong>Vocal/Cry</strong></td>
<td>No cry</td>
<td>Occasional whimpers</td>
<td>Moaning, gentle cry,</td>
<td>Consistent cry that</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>or whimpering</td>
<td>Increases in volume</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>and duration</td>
<td></td>
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<tr>
<td><strong>Facial</strong></td>
<td>Smiling, calm,</td>
<td>Neutral expression,</td>
<td>Occasional tense</td>
<td>Marked distress.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>relaxed</td>
<td>Frowning, occasional</td>
<td>Expression, slightly</td>
<td>Brow bulge, eyes</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Grimace</td>
<td>Negative expression</td>
<td>squeezed shut, open</td>
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<td></td>
<td></td>
<td></td>
<td>(e.g. grimace), brow</td>
<td>mouth, taut tongue,</td>
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<td></td>
<td></td>
<td></td>
<td>bulge, shallow naso-</td>
<td>deepening of</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>labial furrow</td>
<td>nasolabial furrow</td>
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<tr>
<td><strong>Behavioral</strong></td>
<td>Neutral, moves easily,</td>
<td>Easy to console with</td>
<td>Consoles with</td>
<td>Inconsolable; absent</td>
<td></td>
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<tr>
<td></td>
<td>Interacts with people or</td>
<td>holding, position</td>
<td>moderate difficulty;</td>
<td>or disorganized</td>
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<td></td>
<td>environment, strong</td>
<td>change, or sucking;</td>
<td>sucks for very short</td>
<td>sucking; high pitched</td>
<td></td>
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<td></td>
<td>rhythmic suck on</td>
<td>winces when</td>
<td>periods, followed by</td>
<td>cry or scream when</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pacifier</td>
<td>touched/moved</td>
<td>crying; cries out</td>
<td>touched or moved</td>
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<td></td>
<td></td>
<td></td>
<td>when loved/touched</td>
<td></td>
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<tr>
<td>**Body Movement/</td>
<td>Normal motor activity,</td>
<td>Fidgeting; mild</td>
<td>Moderate agitation</td>
<td>Thrashing, flailing,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posture**</td>
<td>baseline</td>
<td>hypertonicity above</td>
<td>or moderate immobility;</td>
<td>incessant agitation</td>
<td></td>
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<td></td>
<td>muscle tone</td>
<td>baseline</td>
<td>intermittently</td>
<td>or strong voluntary</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>flexion; moderate</td>
<td>immobility; pro-</td>
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<td></td>
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<td></td>
<td>hypertonicity above</td>
<td>nounced flexion;</td>
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<td>baseline</td>
<td>strong hypertonicity</td>
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<td></td>
<td></td>
<td></td>
<td>above baseline</td>
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<td><strong>Overall rating</strong></td>
<td>0</td>
<td>1</td>
<td>2</td>
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</table>

APPENDIX B:

INSTITUTIONAL REVIEW BOARD APPROVAL
DATE: November 20, 2003

TO: Linda Hatfield, MS, RNC, CRNP; Nursing

FROM: Kevin Gleeson, M.D., Executive Chair
Institutional Review Board

RE: IRB Protocol No. 2003-315 – Efficacy of Oral Sucrose Analgesia During Routine Immunizations at 6 Weeks and 4 Months of Age

Thank you for your application to the Institutional Review Board (IRB). The above IRB protocol number was assigned for the research and should be included on all future correspondence and documentation. The proposed research met the regulatory criteria for convened board review and was reviewed accordingly. Official approval was granted for this research effective November 19, 2003, and valid until November 17, 2004, at which time IRB reconsideration will be required. This approval includes the following:

- Research Protocol – Grant application, pp. 18-22, received 11/19/2003; Abstract, dated 11/19/2003
- Total entry - One hundred (100) subjects
- Authorization to use protected health information (PHI) – Included in consent form
- Advertisement - None; • Questionnaire - Incorporated into protocol
- Other – Letter to physicians, dated 07/01/2003; Letter to parents, dated 11/19/2003
- IRB member exclusions: No investigators for this research serve on the IRB.

Informed consent and Authorization: Only approved investigators may solicit consent for research participation. Subjects or their representatives must receive a copy of the consent form, and for patients include a copy in the medical record along with the protocol abstract. It is the principal investigator’s responsibility to keep original consent forms/authorizations filed in a secure place and to retain them for six years after termination of research that accesses protected health information (PHI), or for two years after termination if no PHI is accessed. Additional requirements apply for FDA and sponsored trials, which the principal investigator should ascertain, if applicable.

Proposing Changes: Federal regulations require prompt reporting to the IRB of any proposed changes in a research activity and prior approval before changes are initiated, except where necessary to eliminate apparent immediate hazards to the subject. (Submit a Modification Request Form to change an existing investigation.)

Adverse Event Reporting: Serious, life-threatening or unexpected adverse events occurring in subjects participating in this research must be reported immediately to the IRB. (Submit the Adverse Event/Safety Report form.) Report all other adverse events (i.e., mild or expected reactions) on the Progress Report for renewal.

Investigator Resources: The HSPO/IRB web site at www.hmc.psu.edu/hmc-irb provides many resources, including an Investigator’s Handbook, educational information, forms to report on or modify ongoing research, plus the institution’s federal assurances (FWA), IRB compliance statement and other helpful information.

The Institutional Review Board appreciates your efforts to conduct research in compliance with the institutional policies and federal regulations that have been established to ensure the protection of human subjects. Please feel free to communicate any future questions or concerns regarding this research to the IRB via its administrative arm, the Human Subjects Protection Office.

KG 18/11/2003
DATE: November 20, 2003
TO: Linda Hatfield, MS, RNC, CRNP; Nursing
FROM: Kevin Giceson, M.D., Executive Chair
       Institutional Review Board
    Analgesia During Routine Immunizations at 6 Weeks and 4 Months of Age

The Human Subjects Protection Office (HSPO) understands that you wish to exclude Sheila
Smith, MSN, RN, as a co-investigator for this research until she completes the HMC
investigator tutorial.

Attached is your approval memo for the above research.

If you have any questions, please call the Human Subjects Protection Office for assistance.
Thank you.

KGicen
DATE: October 27, 2004

TO: Linda A. Hatfield, Nursing (HMC)

FROM: Kevin Gleeson, M.D., Executive Chair
Institutional Review Board

RE: IRB Protocol No. HY03-315 - Efficacy of Oral Sucrose Analgesia During Routine Immunizations at 6 Weeks and 4 Months of Age

The Human Subjects Protection Office (HSPO) received the progress report for the above titled investigation, with your request for Institutional Review Board (IRB) approval to continue this research. The progress report, protocol and supporting documentation were considered during the continuation review process. Approval was granted to renew this investigation for a twelve-month period, from November 1, 2004 through October 31, 2005. Approval was also granted for the revised consent form (dated 08/11/2004). The deletion of co-investigators Smith, Baker, Suliman, and Polomano was noted. (In accord with IRB policy against voting on one’s own protocol, you did not participate in the decision for this research.)

Please continue to forward all correspondence for the IRB directly to the Human Subjects Protection Office, with the IRB protocol number clearly noted. For research requiring written informed consent, the investigator should keep the original signed consent form, provide the subject with a photocopy, and for patients, include a copy in the medical record along with the research abstract.

Federal regulations require prompt reporting to the IRB of any proposed changes in a research activity and prior approval before changes are initiated, except where necessary to eliminate apparent immediate hazards to the subject. Federal regulations also require that serious, life-threatening or unexpected adverse events occurring in subjects participating in this project be reported immediately to the IRB. These events must be reported on the Adverse Event/Safety Report form. All other adverse events (such as mild or expected reactions) should be reported on the Progress Report for continuing review.

The Institutional Review Board appreciates your efforts to conduct research in compliance with the federal regulations that have been established to ensure the protection of human subjects.

KG\k

An Equal Opportunity University
DATE: October 30, 2005

TO: Linda A. Hatfield, Nursing (HMC)

FROM: Kevin Gleeson, M.D., Executive Chair
Institutional Review Board

RE: IRB Protocol No. HY03-315 - Efficacy of Oral Sucrose Analgesia During Routine Immunizations at 6 Weeks and 4 Months of Age

The Human Subjects Protection Office (HSPO) received the progress report for the above titled investigation, with your request for Institutional Review Board (IRB) approval to continue this research. The progress report, protocol and supporting documentation were considered during the continuation review process. Approval was granted to renew this investigation for a twelve-month period, from November 1, 2005 through October 31, 2006. (In accord with IRB policy against voting on one’s own protocol, L. Hatfield, MS, RNC, CRNP did not participate in the decision for this research.)

Please continue to forward all correspondence for the IRB directly to the Human Subjects Protection Office, with the IRB protocol number clearly noted. For research requiring written informed consent, the investigator should keep the original signed consent form and provide the subject with a photocopy. For clinical treatment protocols, include a copy of the consent form and the abstract in the patient’s HMC medical record to inform other medical caregivers about this research.

Federal regulations require prompt reporting to the IRB of any proposed changes in a research activity and prior approval before changes are initiated, except where necessary to eliminate apparent immediate hazards to the subject. Please request approval for proposed changes using the Modification Request Form. Federal regulations also require the prompt reporting to the IRB of unanticipated problems involving risks to subjects or others. Please report these problems according to the directions in the “Adverse Event Definitions and Reporting Requirements”, using the indicated report form and/or tracking log. (See www.hmc.psu.edu/forms/studies)

The Institutional Review Board appreciates your efforts to conduct research in compliance with the federal regulations that have been established to ensure the protection of human subjects.

KGJbs
APPENDIX C:

CLINICAL TRIALS REGISTRATION
**ClinicalTrials.gov**
Protocol Registration System

**Edit Protocol Record**

Main  Select  Preview  Spelling  Edit All  Delete

Optional Actions:  Reset to In-Progress

**Record Status:** In Progress | Completed | Approved | Released

**Completed**

**Owned by:** LHatfield (lhatfield@psu.edu)  **Last updated:** 09/02/2005 11:32 by LHatfield (lhatfield@psu.edu)

**Initial release:** [not yet released]

**Edit**

**Comments:** None

---

**Edit**

**Unique Protocol ID:** IRB NO. 2003-315

**Secondary IDs:**

**ClinicalTrials.gov ID:**

**Brief Title:** Utilization of Oral Sucrose to Decrease Pain in Infants During Immunizations

**Official Title:** Efficacy of Oral Sucrose Analgesia During Routine Immunizations at 6 Weeks and 4 Months of Age

**IND/IDE Protocol?** No

**Edit**

**Sponsor:** Penn State University

**Collaborators:** Children's Miracle Network

**Review Board**

**Approval Number:** IRB NO. 2003-315

**Board Name:** Penn State Hershey Institutional Review Board and Human Subjects Protection Office

**Board Affiliation:** Penn State College of Medicine, Penn State Milton S. Hershey Medical Center

**Board Chair:** Kevin Gleeson, MD, Professor of Medicine, Director

**Oversight Authorities:** United States: Food and Drug Administration

**Edit**

**Brief Summary:** The study explores the potential benefits of a sugar water solution for decreasing pain in infants during routine immunizations.

**Detailed Description:** Acute pain during early life may alter infant pain responses, cognitive development, and behavioral outcomes. Immunization injections represent a relatively brief exposure
to acute pain, yet assessment studies demonstrate that infants respond with significant distress during the injections. This study will examine the analgesic potential of oral sucrose in diminishing the pain associated with immunization injections in 6 week to 4-month-old infants. The proposed mechanism of action is via the activation of endogenous opioids that attenuate noceceptive information at the level of the dorsal horn.

Comparison: Administration of oral sucrose 2 minutes prior to immunizations compared to administration of sterile water 2 minutes prior to immunizations

**Edit**

**Phase:** N/A

**Study Type:** Interventional

**Overall Status:** Completed

**Record Verification Date:** April 2005

**Study Start Date:** November 2003

**Last Follow-Up Date:**

1. NOTE: Last Follow-Up Date not entered.

**Data Entry Closure Date:**

1. NOTE: Data Entry Closure Date not entered.

**Study Completion Date:**

1. NOTE: Study Completion Date not entered.

**Edit**

**Study Design:**

- **Study Purpose:** Treatment
- **Allocation:** Randomized
- **Masking:** Double Blind
- **Control:** Placebo Control
- **Assignment:** Parallel Assignment
- **Endpoints:** Efficacy Study

**Outcomes:**

- **Primary Outcomes:**
  - The University of Wisconsin Children’s Hospital Pain Scale will measure the primary outcome acute behavioral pain response. Measure will be recorded at baseline, immediately after immunizations and 3 minutes following immunizations
- **Secondary Outcomes:**
  - Duration of analgesia during immunizations
  - Age related changes in behavioral pain response during immunizations

**Edit**

**Conditions:**

- Pain
- Procedural pain

**Keywords:**

- Pain
- Procedural Pain
- Sucrose
Infant
Newborn

**Interventions:** Behavior: Sucrose

**Eligibility Criteria:**

1) currently between 2 and 4 months of age; 2) birth between 37 and 42 weeks’ completed gestation; 3) birth weight greater than 2.5 kg; and, 4) no evidence of acute or chronic disease processes.

Exclusion Criteria:

1) they are experiencing concurrent illness; 2) they received an analgesic/sedative 6 hours prior to the office visit; 3) the infant has been breast fed 30 minutes prior to the visit or wishes to breast feed during or immediately after the immunization; 4) the infant has been introduced to solid food; 5) the infant may not receive a pacifier; 6) the infant is diagnosed with a major congenital disorder where the behavioral responses to painful stimuli may be altered; or, 7) language barriers preclude the process of obtaining parental consent.

**Gender:** Both

**Minimum Age:** 6 Weeks

**Maximum Age:** 4 Months

**Healthy Volunteers?** Yes

**Target Number of Subjects:** 140

**Central Contact:** Linda A Hatfield, PhD(c) CNNP
Telephone: 717 531-1364
Email: lhattfield@psu.edu

**Study Officials/Investigators:** Linda A Hatfield, PhD(c) CNNP
Study Principal Investigator
Penn State College of Medicine, Penn State Milton S. Hershey Medical Center

**Locations:** Facility: General Ambulatory Pediatric Clinic, Penn State Children's Hospital
Hershey, Pennsylvania, United States

Contact: Maryellen Gusie, MD
Telephone: 717-531-8006
Email: mgusie@psu.edu

**Recruitment Status:** Completed

**Citations:**

**Links:**
APPENDIX D:

PHYSICIAN NOTIFICATION LETTER
To: Attending Physicians
University Pediatric Associates

Re: Sucrose Analgesia during Routine Immunizations

Dear Attending Physicians:

I am writing to solicit support with recruitment efforts related to my proposed investigation entitled “Efficacy of oral sucrose analgesia during routine immunizations at 6 weeks and 4 months of age. Findings from this study will make important contributions to research on the analgesic potential of oral sucrose as a pre-procedure intervention for painful episodes and as an adjunctive treatment to maximize analgesia for more prolonged and severe pain states in infants and children.

The proposed plan of study evaluates the analgesia effects of clinically established concentrations of oral sucrose during routine immunization injections in healthy, full term, postnatal infants at 6 weeks and 4 months of age. All groups will receive routine care and support before, during, and after routine immunizations from clinic nurses according to standard hospital procedure. Additionally, each group will participate in one of two study interventions, either the administration of sucrose or the administration of sterile water prior to the combined DTaP containing immunization. Parents of the newborn infants will receive the attached letter in the newborn package describing the study and requesting participation.

For additional details of the study, please reference the attached abstract. If you have any questions or concerns, contact Linda Hatfield, at 531-1364.

Please indicate below your willingness to have your patients recruited for the study.

___________ Yes, I will notify my patients of this study.

___________ No, I will not notify my patients of this study.

Attending Physicians Signature __________________________ Date __________

Thank you for your support with this study.

Sincerely,

Linda Hatfield MS, RNC, CRNP
Nursing Research Specialist
Department of Nursing
APPENDIX E:

PARENTAL NOTIFICATION LETTER
Dear Parents,

You are being offered the opportunity to participate in a research study conducted by Linda Hatfield, MS, RNC, CRNP, in the Department of Nursing, and Maryellen Gusic, MD, Director of General Pediatric Services at the Penn State Children’s Hospital Milton S. Hershey Medical Center, because you have a newborn who will be scheduled to receive a well child care check up in the coming months. During the 2 and 4-month visit your child will receive immunizations. Research has shown that small amounts of sugar water may reduce infant pain during immunizations. The purpose of the study is to increase our knowledge about the pain relieving effects of sugar water during immunizations. Findings from this study will make important contributions to the research on decreasing infant pain. About 100 infants from the pediatric outpatient clinic on Cherry Drive are being asked to participate.

Please contact Linda Hatfield at (717) 531-1364 if you are willing to participate in the study. At your child’s 2-month or 4-month visit, you will talk with Linda who will explain the study details and allow you to ask further questions. If you agree to participate in the study, Linda will ask you to sign a routine consent form allowing your child to swallow either a sugar water or sterile water solution before your child gets their immunizations.

The Penn State Milton S. Hershey Institutional Review Board has approved the project. If you are interested in having your child participate in this study, or would just like to know more about the study, please contact: Linda Hatfield at (717) 531-1364. Your participation in the study is completely voluntary, and your decision to participate or not participate will not in any way affect the care your child will receive here.

Thank you very much for taking the time to consider this very exciting project.

Linda Hatfield MS, RNC, CRNP
Nursing Research Specialist
Department of Nursing

Maryellen Gusic MD
Associate Professor of Pediatrics
Director, General Pediatric Services
University Pediatric Associates
APPENDIX F:

NOTICE TO POTENTIAL PARTICIPANTS
IRB Protocol No. 2003-315

Date: April 8, 2005

________________________________________
Infant’s Name     Physician     Date     Time

_____ Yes, I would like to hear about the sugar water study. Please call me.

Caregiver’s Name________________________ Telephone Number______________

_____ No I am not interested. Please do not call.

Please put this sheet in the envelope at the nurse’s station. Thank you.

Linda
APPENDIX G:

INFORMED CONSENT
Title of Project: Efficacy of Oral Sucrose Analgesia During Routine Immunizations at 6 weeks and 4 Months of Age

Principal Investigator: Linda Hatfield MS, RNC, CRNP

Other Investigators: Co-investigator, Maryellen Gusic, MD
Associate Professor of Pediatrics
Director, General Pediatric Ambulatory Services

Participant’s Printed Name: _____________________________

This is a research study. Research studies include only people who voluntarily choose to take part. This consent form gives you information about this research, which will be discussed with you. This consent form may contain words or procedures that you do not understand. You are urged to ask questions about anything that is unclear to you. Discuss it with your family and friends and take your time to make your decision. You will receive a copy of the signed and dated consent form to keep.

1. Purpose of the Research: Your child is being offered the opportunity to take part in this research because he/she is a healthy full term infant between 6 weeks and 4 months of age who is receiving his/her routine immunizations. The purpose of this research is to obtain information on the safety and effectiveness of sucrose (table sugar dissolved in sterile water) given by mouth, for reducing the pain associated with routine immunizations. Approximately 140 infants will take part in this research; all participants will be enrolled at the Hershey Medical Center.
2. **Procedures to be Followed**: If you agree to participate in the study, your child will participate at their 2 and 4 month immunization visit. The following study procedure will be identical for your child’s 2 and 4-month immunization visit. Your child will receive routine care and support from the clinic nurse before, during, and after your child receives immunizations according to standard hospital procedure. In addition, your child will be assigned by chance (similar to the toss of a coin) to either the oral sugar water study group or the sterile water study. The investigator and you will not know if your child has been assigned to the sugar solution or sterile water group. Your child will lie quietly on the examination table or supported in your lap for five minutes. Before the first injection your child will be given a pacifier. A small amount of the sugar solution or sterile water that was previously drawn up in a syringe will be allowed to trickle down the pacifier. A total of three pain assessments will be obtained, one before, one immediately after the three injections and one three minutes after the injections. In order for your child to stay in the research study, you will be discouraged from holding, cuddling, or breastfeeding your child immediately after the immunizations. You are being asked to refrain from these activities immediately after each immunization because these activities may interfere with the research study. Discouraging parents from holding, cuddling, or breastfeeding their child during immunizations is not standard procedure at Penn State Hershey Medical Center. The assessments will be complete approximately 3 minutes after your child receives his/her first immunization.

3. **Discomfort and Risks**: Your child will be assigned to a treatment group by chance. The treatment your child receives may prove to be less effective than the other research treatment. There is a possibility that your child may choke, cough, or vomit following the administration of the study solution. To minimize these occurrences, the nurse will closely monitor your child.

4. **Benefits**
   a. **Possible Benefits to Your Child**: The possible benefit your child may experience from the sugar solution described in this research is a decrease in the intensity and/or amount of discomfort experienced during immunization injections. No benefits are guaranteed.
b. **Possible Benefits to Society:** Your child’s participation in the study may help determine the pain relieving potential of oral sucrose for short and prolonged pain in infants and children.

5. **Other Options That Could be Used Instead of this Research:** You may decline your child’s participation in the research and receive routine care and support according to standard hospital procedures. Because it is experimental, the therapy offered in this research is only available to your child if your child takes part in the research study.

6. **Time Duration of the Procedures and Study:** Your child’s participation in the study is expected to be approximately 15 minutes. Five minutes for the study procedure and 10 minutes for questions. The same time will be required for your child’s participation at the 4-month immunization visit. The duration of the study will be approximately 1 year.

7. **Statement of Confidentiality:**

   Health information about your child will be collected because your child is a part of this research study. By signing this form, you are allowing the people and groups that are listed in the next paragraph to use your child’s health information for purposes related to this research. You are also allowing these groups to share your child’s health information with other specific groups for their use as part of this research study. Your child’s information will only be used or shared as explained in this consent form or when required by law.

   The research team may use the following sources of health information:
   - Prenatal and current health history as documented in your child’s computer and written medical record and as given by you
   - Physical and behavioral exam
   - Results of the pain assessments
   - Follow up interview

   However, there may be other health information that is not listed here. Your child’s health information may be used or shared with other specific people or groups in connection with this research study. Research records that identify your child will be kept confidential as required by law. Your child will not be identified by name, social security number, address, phone number, or any other direct personal identifier in
research records given to someone outside of The Milton S. Hershey Medical Center (HMC) or Penn State College of Medicine (PSU), except when required by law. Your child’s research records will be labeled with a code number. The list that matches your child’s name with the code number will be kept in a locked file in Linda Hatfield’s office.

Representatives of the following people/groups within HMC/PSU are allowed to use and share your health information with other specific groups in connection with this research study:

- The principal investigator, Linda Hatfield, MS, RNC, CRNP
- Co-investigator, Maryellen, Gusic, MD
- Associate Professor of Pediatrics
- Director, General Pediatric Ambulatory Services
- Cheston Berlin, MD
- Professor of Pediatrics, and Pharmacology
- Judith Hupcey, Ed.D. CRNP
- Associate Professor of Nursing
- Mary Beth Clark, Ed.D. RN
- Assistant Professor of Nursing
- Vernon Chinchilli, PhD
- Distinguished Professor and Chair of Health Evaluation Sciences
- The HMC/PSU Institutional Review Board,
- The HMC/PSU Human Subjects Protection Office,

The people or groups listed in the above paragraph may share your health information with the following persons and organizations outside HMC/PSU for their use in connection with this research study:

- The Office of Human Research protection in the US Department of Health and Human Services
- Study Tool Consultant, Teresa Pellino, PhD, RN from the University of Wisconsin Hospital and Clinic
- Children’s Miracle Network

Your child’s information may be shared with groups not listed here if the people who receive your child’s health information are not required by law to protect the privacy of the information.

Your permission for the use and sharing of your child’s health information will expire upon completion of the research study. At that time, the research information not
already in your child’s medical record will be destroyed. Any research information in
your child’s medical record will be kept indefinitely.

People usually have a right to access their medical records. However, while the
research is in progress, you may not be allowed to see or copy certain research
information collected in connection with your child’s participation in this research study.
This condition will be effective for the period of the research, and you will be allowed to
see this portion of your child’s records when the whole research project is complete.

The research-related therapy cannot be provided unless you allow the use and
sharing of your child’s protected health information that is collected during your child’s
participation in this research study. If you wish your child to participate in this research,
you must sign this form. If you do not wish your child to participate, your child will
receive the standard medical care as decided by your child’s physician.

You are free to withdraw your permission for the use and sharing of your child’s
health information, but you must do this in writing as indicated in the HMC Privacy
Notice. If you do decide to withdraw, we ask that you contact Linda Hatfield in writing
and let her know that you are withdrawing your child from the research study. Her
mailing address is:

Linda Hatfield MS, RNC, CRNP
Nursing Research Specialist, Outcomes Research
Department of Nursing
Academic Support Building, Mail Code A250
Penn State Milton S. Hershey Medical Center, Box 855
600 Centerview Road
Hershey, Pennsylvania 17033-0855

If you withdraw your permission, we will no longer use or share medical
information about your child for the reasons covered by your written authorization,
except when the law allows us to continue using your child’s information. We are
unable to take back anything we have already done or shared with your permission
and we may continue using and sharing the information obtained prior to your
withdrawal as necessary to maintain the soundness of the overall research. Also, we
are required to keep our records of the care that we provided to your child as long as
the law requires.
In the event of any publication resulting from the research, no personally identifiable information will be shared.

8. **Right to Ask Questions:**

You have the right to ask any questions you may have about this research. If you have questions or concerns later or if you believe your child may have developed an injury that is related to this research, you should contact Linda Hatfield, MS, RNC, CRNP at 717-531-1364.

If you have questions regarding your child’s rights as a research participant, you may contact the research protection advocate in the HMC Human Subjects Protection Office at 717-531-5687.

If you have questions or concerns regarding your child’s privacy and the use of your child’s personal health information, please contact Jim Bifano, the HMC Privacy Officer, at 717-531-8059.

9. **Reimbursements and/or Costs for Participation:**

There is no payment or cost to you for participation in the research study. It is possible that your child could develop complications or injuries as a result of participating in this research study. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. It is the policy of this institution to provide neither financial compensation nor free medical treatment for research-related injury. You are not waiving any legal rights you may have by signing this form.

Costs for the treatment of research-related injuries will be charged to your insurance carrier or to you. Some insurance companies may not cover costs associated with research studies. If for any reason these costs are not covered by your insurance, they will be your responsibility.

10. **Research Funding:** The institution and investigators have received a grant from Children’s Miracle Network to support this research.
11. **Voluntary Participation**: Taking part in this research study is voluntary. If you choose to allow your child to take part in this research, your major responsibilities will include:

   a. Being available for a follow up telephone interview the next day, and
   b. Notifying the principle investigator of your questions and concerns regarding your child’s participation in the study.

Your child does not have to participate in this research. If you choose to allow your child to take part, you have the right to stop your child’s participation at any time. If you decide not to allow your child to participate or if you decide to stop your child’s participation in the research at a later date, there will be no penalty or loss of benefits to which your child is entitled. In other words, your decision not to permit your child to participate in this research or to stop taking part in the research will not affect your child’s medical care.

   During the course of the research, you will be informed of any new findings that may affect your willingness to continue your child’s participation in this research.

**Signature and Consent to be in the Research**

Your signature below means that you have read the above information about this research study and have asked the questions you currently have about the research. By signing this consent form, you indicate that you consent to, and give permission for, your child to take part in this research study and that you have had the opportunity to ask questions and that those questions have been answered.

<table>
<thead>
<tr>
<th>Signature of Parent or Guardian</th>
<th>Date</th>
<th>Time</th>
<th>Printed Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature of person who explained this research*</td>
<td>Date</td>
<td>Time</td>
<td>Printed Name</td>
</tr>
</tbody>
</table>

(*Only approved investigators for this research may explain the research and obtain informed consent.*)
APPENDIX H

DATA COLLECTION SHEET
## Sucrose Study - Phase 2

**Study Number**

### History
- **Date of Birth**: DD / MM / YYYY
- **Gestational age at birth**: 
- **Gender**: ○ Male ○ Female
- **Birth Weight**: lbs ___ oz ___
- **Type of Delivery**: ○ Spontaneous vaginal ○ Vacuum assisted ○ Forceps assisted ○ Breach ○ Cesarean Section
- **Multiple birth?**: ○ Yes ○ No
- **Study Group**: ○ A ○ B
- **Nutrition**: ○ Breast ○ Bottle
- **Prior painful procedures**: ○ Circ ○ Bili ○ Vit k ○ Hep ○ PKU ○ Other
- **Anesthesia?**: ○ Yes ○ No

### Administration of Solution

<table>
<thead>
<tr>
<th>Time</th>
<th>Description</th>
<th>Pain Assessments*</th>
</tr>
</thead>
</table>
| 0 Minutes | Behavior state at beginning of session
○ Calm, relaxed
○ Agitated, distressed, fussy
○ Crying, inconsolable
○ Infant refused solution? ○ Yes ○ No
○ Immediate adverse events ○ No ○ Yes |
| 2 Minutes | Combined Injection, HIB, PCV7 (2 minutes after administration of solution) |
| 5 Minutes | Recovery (3 minutes after administration combined injection) |

### Dosage
- 0.5 ml/kg - ________ cc

*Baseline pain assessment - 0 Minutes
Other pain assessments immediately after injection
APPENDIX I

PERMISSION TO REPRODUCE

GATE CONTROL THEORY OF PAIN
Permissions Letter

DATE: Tuesday, February 21, 2006

TO: Linda Hatfield
   Penn State University, Specialist, Nursing Research
   1135 Stonegate Rd.
   Hummelstown, PA 17036

FROM: Elizabeth Sandler, Rights and Permissions

RE: Your request for permission dated 02/21/06

Regarding your request, we are pleased to grant you non-exclusive, non-transferable permission to use the AAAS material identified below in your dissertation or thesis identified below, but limited to print and microform formats only, and provided that you meet the criteria below. Such permission is for one-time use and therefore does not include permission for future editions, revisions, additional printings, updates, ancillaries, customized forms, any electronic forms, braille editions, translations, or promotional pieces. We must be contacted for permission each time such use is planned. This permission does not apply to figures/artwork that are credited to non-AAAS sources. This permission does not include the right to modify AAAS material.

Print the required copyright credit line on the first page that the material appears: "Reprinted (abstracted/excerpted) with permission from [FULL REFERENCE CITATION]. Copyright [YEAR] AAAS." Insert the appropriate information in place of the capitalized words.

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Permission is valid for use of the following AAAS material only:
Fig 4 from Melzack & Wall, SCIENCE 150:971-981 (1965)
In the following work only:
PhD dissertation of Linda Hatfield

Thank you for writing. If you have any questions please call me at (202) 326-6765 or write to me via fax at (202) 682-0816. For international calls, +1 is the country code for the United States.

Headquarters:
1200 New York Avenue, NW, Washington, D.C. 20005 USA
APPENDIX J:

PERMISSION TO REPRODUCE

UNIVERSITY OF WISCONSIN PAIN SCALE
February 8, 2006

Linda Hatfield MS, RNC, CRNP
Nursing Research Specialist- Outcomes Research
Department of Nursing
Academic Support Building
Mail Code A250
Penn State Milton S. Hershey Medical Center, Box 855
600 Centerview Road
Hershey, Pennsylvania 17033-0855

Dear Ms. Hatfield:

In response to your request, permission is granted to reprint Table 1 from the article Assessment of the validity and reliability of The University of Wisconsin Children's Hospital pain scale for preverbal and nonverbal children that appeared in Pediatric Nursing Journal, November/December 1999 issue, provided the fee of $50 is prepaid directly to Pediatric Nursing and the following permission line is used.

Adapted from Pediatric Nursing, 1999, Volume 25, Number 6, pp. 672. Reprinted with permission of the publisher, Jannetti Publications, Inc., East Holly Avenue Box 56, Pitman, NJ 08071-0056; Phone (856) 256-2300; FAX (856) 589-7463. For a sample copy of the journal, please contact the publisher.

If you have any questions, please contact me at (856) 256-2346.

Sincerely,

Katie Brownlow Editorial Coordinator Anthony J.
Jannetti, Inc. East Holly Avenue/Box 56 Pitman, NJ 08071-0056
FAX: 856-256-2345

https://access.hersheymed.net/servlet/webacc,DanaInfo=.awfdpenrGpnl3trAluuR6... 2/18/2006
APPENDIX K:

PERMISSION TO REPRODUCE

AFFERENT FIBERS TABLE
Hi Linda,

Thanks for your email. Permission has been granted to use table 1 from the article listed below. Please ensure that you give full acknowledgement to the original source of publication.

With best wishes,
Adrienne
Hanratty
Reprints/permissions
BioMed
Central Ltd

From: Linda Hatfield [mailto:linda_hatfield@comcast.net]
Sent: 28 January 2006 20:44
To: 05: BMC Info
Subject: Permission to reproduce

I would like to have permission toadapt table 1 from

**Selective activation of primary afferent fibers evaluated by sine-wave electrical stimulation**
Koga K, Furue H, Rashid MH, Takaki A, Katafuchi T, Yoshimura M

This work will appear in my doctoral thesis. Linda Hatfield

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Linda Hatfield
lhatfield@psu.edu

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Awards, Scholarship
2005 Elizabeth Carlino Education in Nursing Scholarship Award
2004 Janet A. Williamson Graduate Scholarship Award in Nursing
2003 Aventis Pasteur/American Nurses Foundation Scholar
1997 Phi Kappa Phi
1985 Sigma Theta Tau

Research Support
2005 The analgesic properties of oral sucrose during routine immunizations. Are there age related changes in behavioral pain response in infants at 2 and 4 months of age? Funded by the Children’s Miracle Network. Award $8,375.00.
2003 The efficacy of oral sucrose analgesia during routine immunizations at 2 and 4 months of age. Funded by the American Nurses Foundation. Grant # 2003051. Award $5,485.00.

Professional Presentations
2. Feb. 26, 2005 Utilization of Sucrose as a Pre-procedural Analgesic In Infants And Young Children. Sigma Theta Tau Spring Research Day. Pennsylvania State University, University Park, PA

Peer Reviewed Publications

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