

1997

Comparison of the Effectiveness of Intradermal Injection of Lidocaine, Iontophoretic Delivery of Lidocaine, and Topical Emla Cream as Local Anesthetics for Venipuncture

Carol Straight
Grand Valley State University

Follow this and additional works at: <https://scholarworks.gvsu.edu/theses>



Part of the [Nursing Commons](#)

ScholarWorks Citation

Straight, Carol, "Comparison of the Effectiveness of Intradermal Injection of Lidocaine, Iontophoretic Delivery of Lidocaine, and Topical Emla Cream as Local Anesthetics for Venipuncture" (1997). *Masters Theses*. 421.

<https://scholarworks.gvsu.edu/theses/421>

This Thesis is brought to you for free and open access by the Graduate Research and Creative Practice at ScholarWorks@GVSU. It has been accepted for inclusion in Masters Theses by an authorized administrator of ScholarWorks@GVSU. For more information, please contact scholarworks@gvsu.edu.

COMPARISON OF THE EFFECTIVENESS
OF INTRADERMAL INJECTION OF LIDOCAINE,
IONTOPHORETIC DELIVERY OF LIDOCAINE,
AND TOPICAL EMLA CREAM AS LOCAL
ANESTHETICS FOR VENIPUNCTURE

By

Carol Straight

A THESIS

Submitted to

Grand Valley State University

in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN NURSING

Kirkhof School of Nursing

1997

Committee Members:

Jean Nagelkerk, R.N., Ph.D.

Timothy Esser, M.D.

Michelle Arthur, R.N., M.S.N.

Terry Bauman, Pharm.D.

ABSTRACT

COMPARISON OF THE EFFECTIVENESS OF INTRADERMAL INJECTION OF LIDOCAINE, IONTOPHORETIC DELIVERY OF LIDOCAINE, AND TOPICAL EMLA CREAM AS LOCAL ANESTHETICS FOR VENIPUNCTURE

By

Carol Straight

This study was undertaken to establish whether the administration of a local anesthetic, lidocaine, significantly reduces the pain of venipuncture in adults, to establish the degree of tolerability and effectiveness of each of three delivery methods for lidocaine, and to identify recipient's preferences among the three pain-relieving measures. In this study, lidocaine was administered using three different delivery techniques: (1) intradermal injection of lidocaine, (2) iontophoresis of lidocaine, and (3) topical application of lidocaine/prilocaine cream, prior to undergoing venipuncture. Participants were asked to measure the level of pain experienced with each method of local anesthesia as well as the level of pain experienced with venipuncture following each local anesthetic. Each of the three treatment groups were compared with placebo and each participant served as his or her own control. Twenty-two volunteers were recruited for participation in this study. Twenty volunteers completed two treatment sessions and twelve volunteers completed three treatment sessions.

Table of Contents

List of Tables.....	iv
List of Figures.....	v
List of Appendices.....	vi
CHAPTER	
1 INTRODUCTION.....	1
2 CONCEPTUAL FRAMEWORK AND LITERATURE REVIEW.....	5
Conceptual Framework.....	5
Literature Review.....	10
Assessment of Pain.....	30
Summary.....	31
Research Hypothesis.....	32
Definition of Terms.....	32
3 METHODOLOGY.....	34
Study Design.....	34
Sample and Setting.....	34
Instruments.....	35
Procedures for Data Collection.....	37
Human Subject Consideration.....	42
4 RESULTS.....	43
Results of Surveys.....	43
Hypothesis Testing.....	45
5 DISCUSSION/LIMITATIONS/IMPLICATION.....	54
Discussion.....	54
Relationship to Theoretical Framework.....	56
Strengths, Limitations, and Recommendations.....	58
Conclusions.....	59
6 REFERENCES.....	68

List of Tables

Table 1. Influence of Treatments Upon Mean Venipuncture Pain.....	49
Table 2. Comparison of Pain in Treated Venipuncture.....	50
Table 3. Summary of Pain Experienced With Anesthesia and Venipuncture.....	52

List of Figures

Figure 1	Model of Betty Neuman's Systems Theory.....	6
Figure 2	Integration of Sensory Pain Pathway with Neuman's Systems Theory.....	8
Figure 3	Lidocaine Molecule.....	12
Figure 4	Iontophoresis of Lidocaine.....	19
Figure 5	EMLA Cream.....	26

List of Appendices

A	Visual Analog Scale.....	61
B	Questionnaire.....	62
C	Informed Consent.....	63
D	Life-Tech Inc. Instruction on Use of Needle Buster.....	66
E	Astra Pharmaceutical Instruction on Use of EMLA Cream.....	67
F	Permission for Reprint.....	68

CHAPTER ONE

INTRODUCTION

Pain elimination and management is one of nursing's major responsibilities. Pain control is particularly important in hospital settings where patients frequently encounter uncomfortable procedures. One of the most common hospital procedures is venipuncture. For the clinician who initiates venipuncture, the procedure is seemingly benign. To the recipient, a venipuncture may be an uncomfortable and anxiety-provoking event experienced during the hospital course.

Intravenous cannulation is one of a handful of invasive procedures typically within the sole domain of nursing. Nursing has historically sought-out caring and comfort measures for patients, yet, has produced limited research-based remedies to lessen the aversion of intravenous insertion (IV). There is a substantial body of medical research revealing the safety and efficacy of painless or nearly-painless venipuncture using a local anesthetic with a host of different delivery techniques: intradermal injection, iontophoresis, and topical anesthetic creams.

Dentists administer more local anesthetics annually than are given by all other medical specialties combined (Chrichton, 1992). Pain-control is so fundamental in dentistry that a large part of dental training is dedicated to local anesthesia. If one can allow an analogy between the discomfort experienced during tooth filling with the discomfort during introduction of a large-bore intravenous catheter, it is curious that most nursing textbooks on IV therapy only recommend holding the skin taught as a means of reducing pain (Dick et al., 1992).

There may be several explanations for clinicians reluctance to use pain reducing techniques during IV insertion: (1) There may be a belief that venipuncture

results in little discomfort and is well tolerated, (2) there may be a concern that use of a local anesthetic exposes an individual to potential allergic or toxic reactions, (3) there may be a belief that the pain-reducing intervention may produce greater discomfort than the venipuncture itself.

Patients undergo many painful procedures and are frequently undertreated for their pain. Reducing pain during procedures in an effort to advocate for a patient's well-being is a crucial part of the clinician's role. However, the topic of pain conjures such a wide array of genetic, cultural, and social forces for both patients and clinicians, the intent to expel suffering is often clouded. The biggest obstacle to eliminating procedural-pain may be lacking communication by both patients and clinicians. Stoic silence in the face of pain is still viewed as a sign of strength in many cultures (cited in Jaurez, 1997). Clinicians engrossed in the technicalities of procedures thought to be brief and mildly invasive, may be completely unaware of their patient's pain.

Cooperation from an adult during venipuncture is common as adults can reason the pain will be over soon. Asking a child to hold his or her arm stationary during insertion of a needle is asking behavior contradictory to human neurophysiology. According to sensory pain theory, when abundant nociceptors located in the skin are stimulated by puncture from a needle, fast afferent sensory fibers (A fibers) carry the stimulus to the dorsal horn of the spinal cord where synapse occurs with an efferent motor neuron. Efferent motor fibers rapidly travel from the spinal cord to the muscle(s) of the affected region causing retraction of the injured body part. This occurs instantly, before the neospinothalamic and paleospinothalamic tracts carry the painful stimulus to the midbrain, postcentral gyrus, and cortex, where the pain is realized (Ludwig-Beymer, Huether, & Schoessler, 1994). If the specific pain stimulus is repeated or perceived as extra-ordinary, a new and permanent pain reflex arc may

be created (St. John, 1995).

Neuman's Systems Theory describes environmental forces or stressors with which individuals struggle. Venipuncture is a stressor producing both anxiety and pain. Contending with such stressors consumes an individual's energy stores leaving less reserve for contending with other stressors. The goal of nursing practice, according to Neuman's Systems Theory, is to reduce or eliminate stressors before they produce symptomology in an attempt to maximize an individual's energy. Neuman's Theory subscribes to a greater level of wellness for an individual when noxious environmental stressors are eliminated and energy reserves are heightened (Neuman, 1989).

Purpose

This study was undertaken to establish whether the administration of a local anesthetic, lidocaine, significantly reduces the pain of venipuncture in adults, to establish the degree of tolerability and effectiveness of each of three delivery methods for lidocaine, and to identify recipient's preferences among the three pain-relieving measures. In this study, lidocaine was administered using three different delivery techniques: (1) intradermal injection of lidocaine, (2) iontophoresis of lidocaine, and (3) topical application of lidocaine/prilocaine cream, prior to undergoing venipuncture. Participants were asked to measure the level of pain experienced with each method of local anesthesia as well as the level of pain experienced with venipuncture following local anesthesia.

This research study is significant in that it may demonstrate a safe and effective method(s) for eliminating venipuncture pain. According to Neuman's Systems Theory, eliminating this noxious stressor will afford an individual a greater sense of

wellness. This study is the first step in evaluating the efficacy of infiltrated lidocaine, iontophoresed lidocaine, and topical lidocaine/prilocaine cream, as local anesthetics for a host of other pain-provoking procedures experienced by patients in both hospital and outpatient settings.

Safety and efficacy of this study using an adult sample was established. This study may serve to be precursory to future clinical trial(s) enrolling hospitalized adults and children undergoing multiple or sequential pain-provoking medical procedures.

CHAPTER TWO

CONCEPTUAL FRAMEWORK AND LITERATURE REVIEW

Conceptual Model

Betty Neuman's Systems Theory is a nursing model commissioning the nurse with the responsibility to identify and eliminate unhealthy stressors. The model describes the individual as a dynamic and open system in constant interaction with both internal and external environmental forces which she calls stressors (Neuman, 1995). Contending with stressors consumes client-system energy. Responding to stressors (resulting in asymptomatic and non-adaptational behaviors) and reacting to stressors (resulting in symptomatic and adaptational behaviors) is dependent upon the degree of evolution and integration among three client-system composites: (1) the person's basic core which includes genetic makeup, interrelational patterns, and energy resources, (2) a mold of each individual's physiological, psychological, sociocultural, developmental, and spiritual variables, and (3) three mechanisms or lines of defense protecting the client-systems's basic core (Neuman, 1989). Neuman's Systems Model is depicted in figure 1.

If the outermost flexible line of defense successfully "responds" to a stressor, client-system homeostasis is preserved. In this case, a stressor was thwarted far before provoking manifestations of its' presence (symptoms). If a stressor breaks through the outer line of defense, the client-system "reacts" and there is consequential symptomology. At this point the adaptational normal line of defense is activated mobilizing internal forces to overcome the stressor. If the client-system effectively defends against the stressor, "attainment" of a higher level of resilient

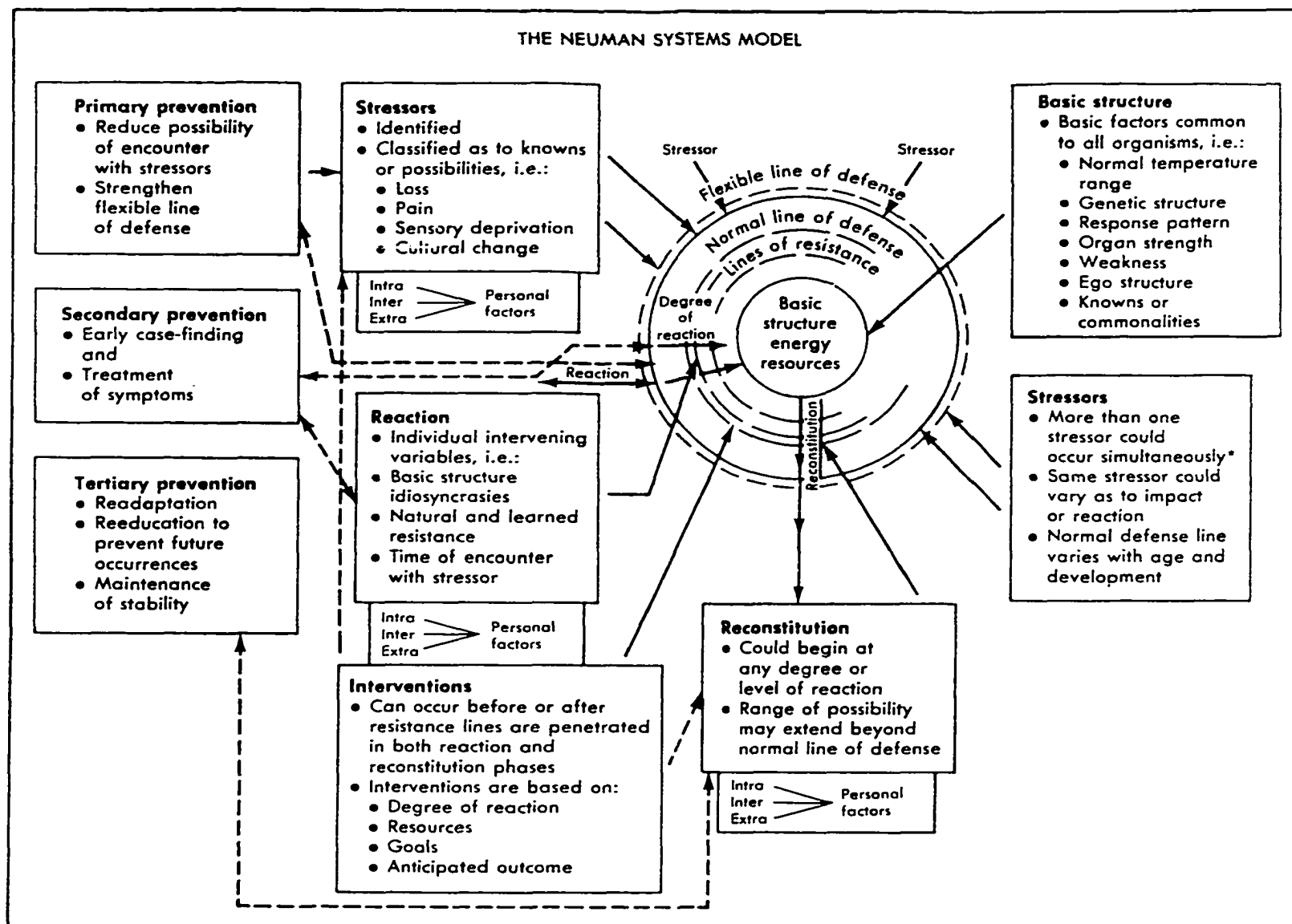


Figure 1. The Neuman Systems Model as it appeared in 1970. Permission for reprint from Appleton & Lange Publishing Company.

homeostasis occurs as the individual has adapted or acquired new coping skills for that particular stressor. If the normal line of defense falters, the innermost line of defense called the the line of resistance is activated. The line of resistance protects the individual's basic core by mobilizing internal forces to overcome the stressor. Once the stressor has been arrested, the client-system may return to its' former level of homeostasis with the environment (maintainment) or the client-system may achieve a higher functioning level of homeostasis with the environment (attainment). The degree of client-system homeostasis is the individual's level of wellness for that given time (Neuman, 1989).

According to Neuman's Systems Theory, the goal of nursing practice is to eliminate or modify stressors, preferably at the flexible line of defense, in order to conserve system's energy for its most judicious use (Smith, 1990). Secondary interventions are intended to eliminate stressors after symptomology has occurred while the goal of tertiary intervention is to "retain" the individual's current level of homeostasis (wellness) or "attain" a higher level of wellness.

Venipuncture is a stressor. It provokes symptomology, pain, therefore it is a noxious stimulus which has bypassed the client-system's flexible line of defense and is operational at the normal line of defense. Physiologic responses to pain include an increase in heart rate, blood pressure, and respiratory rate. Addressing the stressor of venipuncture at this juncture is secondary intervention according to Neuman's Systems Model. As will be discussed in more detail later, the vasovagal trait, is an idiosyncratic physiologic reaction to pain whereby there is sudden and marked bradycardia and hypotension occasionally culminating in syncope. At this juncture, the stressor has activated the individual's line or resistance and is threatening the individuals 's basic genetic and physiological core. There is risk of damage to client-system integrity resulting in a lower level of homeostasis with the

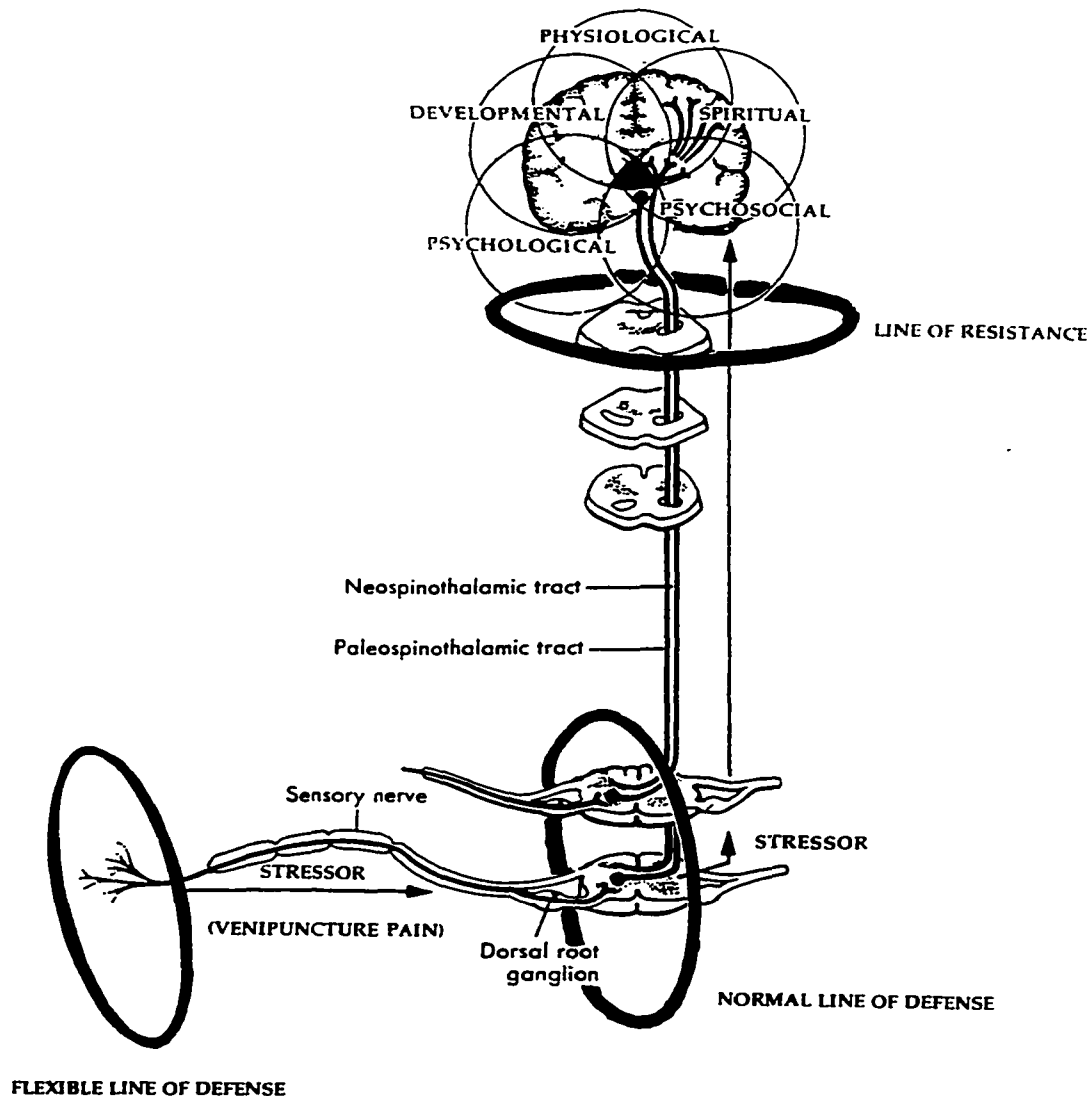


Figure 2. Integration of Neuman's System Model with the Sensory Pain Pathway. In this depiction, venipuncture is a stressor which initially threatens the flexible line of defense where nerve endings (meissner's corpuscles in skin and pacinian corpuscles in subcutaneous tissue) are located. Primary nursing intervention would eliminate venipuncture pain before it had started! Without local anesthesia of these nerve endings, pain will occur along with associated symptoms including increased heart rate, increased blood pressure, muscle tension, and a sense of anxiety. At this point, the normal line of defense has been activated as the noxious pain stimulus has been transmitted to the dorsal horn of the spinal cord. An efferent motor response causes immediate muscle retraction of the body part being punctured. Secondary nursing intervention such as verbal comforting might help in attenuating the symptoms. As the neospinothalamic and paleospinothalamic nerve fibers shoot the pain stimuli to pain centers in the brain, a vasovagal reflex (genetic trait in needle phobia) may be triggered. At this point, the individual's line of resistance has been activated. Tertiary nursing is aimed at preventing syncope, or restoring hemodynamic stability should syncope occur.

environment (wellness). See figure 2.

The Neuman Systems Theory describes another key element of the model called the created environment. The created environment is an unconscious deployment of all client-system variables in order to create apparent system stability in the face of unmanageable adversity. The created environment offers temporary protection for the individual but consumes considerable energy in the process. When the energy spent maintaining the individual's created environment results in energy deficits for other system processes, the created environment may move the individual further from homeostatic health. An individual's created environment can manifest itself by changes in response patterns to stressors, for example the use of denial (Neuman, 1989). As will be presented later, there is evidence that phlebotomy, venipuncture, and other needle associations, are so feared by a segment of the population, that routine and even compelling medical care are avoided (Hamilton, 1996). According to Neuman's Systems Theory, when needle-fear leads to avoidance behaviors and denial of need for health care, the client-system moves further from homeostasis with the environment.

Eliminating venipuncture-associated pain stops the stressor at the flexible line of defense, preventing pain and its associated physiologic manifestations. For infants and children, eliminating venipuncture-associated pain may prevent temporary or permanent establishment of needle phobias. Eliminating venipuncture pain prevents emotional distress which taps client-system energy stores. Children as well as adults receiving venipuncture, are often in a position where it is strategic to spare client-system energy for judicious use opposing more serious stressors. For victims of needle phobia, eliminating venipuncture pain, eliminates a barrier to regular health care, a necessary ingredient for client-system homeostasis. The following is a review of the literature exploring the safety and efficacy of local

anesthesia for venipuncture.

Literature Review

A Belief That Venipuncture is Well Tolerated

It may be a common belief that for the vast majority of persons, venipuncture produces only minor discomfort and anxiety. However, it is estimated that 10% of the population is affected by needle phobia, a newly defined medical condition (Hamilton, 1995). Needle fear, in its severest form, results from an inherited vasovagal reflex which in rare cases has led to shock and death (Galena, 1992). More typically, needle fear produces tachycardia and hypertension followed by bradycardia and hypotension upon needle insertion. These physiologic changes are accompanied by pallor, diaphoresis, lightheadedness, weakness, syncope or near-syncope (Engel, 1978).

Needle fear is thought to be an evolved inherited trait in response to our species' history of death by piercing, stabbing, and cutting injuries. Skin penetration wounds are produced from teeth, claws, and tusks of animals as well as spears, arrows, swords, axes, knives and bullets from humans (Ellinwood & Hamilton, 1991). The corpus striatum is our species' most effective barrier against harmful external stimuli. The absolute thickness of the corpus striatum ranges from 1.0 to 2.0 millimeters with males having slightly thicker skin (Coats & Lupin, 1995).

There is evidence of a learned component to needle fear. In one study of 56 persons with needle phobia, 52% traced their fear to a negative experience at a doctor's or dentist's office at the group's mean age of 8 years. Another 24% experienced vicarious conditioning at seeing another child, often a sibling, demon-

strate a negative reaction to needles (Ost, 1991). The fear of needles may become generalized to include fear of needle-associations such as doctors, nurses, dentists, blood, examination rooms, hospitals, and even the antiseptic odor of offices and hospitals (Marks, 1988).

Needle fear is a physiological as well as psychological stressor. Along with altered cardiovascular hemodynamics, several stress hormones have been found to rise during needle stimulation. Increased cortisol and corticotropin levels have been documented with venipuncture (Rose & Hurst, 1975). Serum epinephrine and norepinephrine levels are known to sharply rise than fall with needle stimulation (Taggart, Hedworth-Whitty, Carruthers, Gordon, 1976). Antidiuretic hormone (ADH) (Ellinwood, 1991) and renin, (Goldstein et al., 1982), become elevated during needle insertion, with ADH rising as high as forty six times the normal value. These rises are probably secondary to the decrease in intravascular volume associated with the marked bradycardia and hypotension of the vasovagal reflex.

Needle fear may serve as a barrier to receiving health care. Individuals with needle fear tend to avoid health care even when the need for medical attention is compelling. In a survey completed by 184 teenage women after delivery, 22% admitted to difficulty seeking prenatal care and associated this to a fear of having blood drawn (Cartwright et al., 1993).

With the incidence of needle phobia estimated to be 10% of the population, it is highly suspicious that a larger hidden population may avoid regular health care secondary to fear of needle puncture. There appears to be evidence that needle insertion may be more than just a routine and benign procedure to some. The recognition and acceptance of needle fear by health care providers is the first step in eliminating this potential stressor and barrier within our health care systems.

A Belief That Allergies or Toxicity May Occur With the Use of Local Anesthetics

Fear of exposing patients to a potential drug reaction such as an allergic reaction or systemic toxicity may be another common explanation for the hesitancy by clinicians to use a local anesthetic to attenuate the pain associated with venipuncture. Lidocaine is a local anesthetic commonly used since its release for use in medicine and dentistry in 1948. The chemical name is 2-diethylamino-N-2, 6-dimethylphenyl-acetamide. It's molecular structure consists of an aromatic ring, which is strongly lipophilic, joined by an ester and a nitrogen-containing aliphatic chain which is strongly hydrophilic (Costello, 1993). See figure 3.

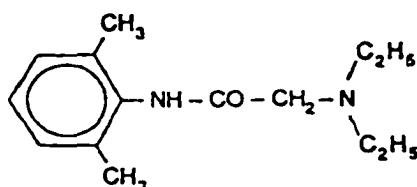


Figure 3. Lidocaine molecule having an aromatic ring, an ester, and aliphatic chain.

Lidocaine is manufactured in a three-step process. 2, 6-dimethylamine is reacted with chloroacetyl chloride yielding N-chloroacetyl-2, 6-xyladine. This in turn is reacted with diethylamine to form lidocaine.

Local anesthetics of the amide type are weak base solutions comprised of charged and uncharged particles. As the acidity of the amide anesthetic increases, there is an increase in the amount of charged solution creating a more stable drug with a shelf life of three to four years. As the acidity of the solution decreases, there is a greater uncharged portion of the solution, resulting in an unstable form easily subject to denaturing reactions such as photodegradation and aldehyde formation. Therefore, lidocaine having a pK of 7.4, has been manufactured with an adjusted pH of 5.0 to 6.5 to enhance shelf-life (PDR, 1995).

There are a variety of commercially-prepared single-dose and multi-dose vials available in 0.5%, 1%, 2%, and 4% strengths of lidocaine for percutaneous and intravenous administration. Multi-dose vials require the addition of an antimicrobial agent for preservation. Typically, one milliliter of lidocaine contains 1 mg of methyl-paraban (MPF) for antiseptic preservation. Allergies to MPF are rare but known. Single-dose vials of lidocaine can be obtained MPF-free. Lidocaine solutions are also available with epinephrine, a vasoconstrictor, which when added to lidocaine, yields higher local tissue levels resulting in greater degree and duration of anesthesia (PDR, 1995).

The exact pharmacology of lidocaine is unclear. It appears lidocaine inhibits ion flux at the neuronal membrane interfering with initiation and conduction of impulses. It is the lipophilic region of the lidocaine molecule as well as the uncharged portion of the drug that is essential in allowing the molecules to enter the neuronal cell membrane or myelin sheath where it exerts a local anesthetic effect by interference with ion flux during cellular depolarization (Costello, 1992).

The recommended dosages for percutaneous administration of lidocaine (without epinephrine) are from 5 to 300 mg of a 0.5% or 1% concentration. Recommended dosages of lidocaine given percutaneously in children over three years of age are 1.5 to 2.0 mg./lb. with a maximum total dosage of 100 mg (PDR, 1995). Typically, infiltration of amide anesthetics exert local anesthesia from 5 to 15 minutes after injection (Christoph, Buchanen, Begalla, Schwartz, 1988 and Farley, Hustead, Becker, 1994).

Approximately 85% of Lidocaine is metabolized in the liver through N-dealkylation. The breakdown metabolites of lidocaine are monoethylglycinexylidide and glycinexylidide, which are less potent than lidocaine, but still may exert an anesthetic effect. The remainder of lidocaine is excreted intact by the kidneys. The elimin-

ation of lidocaine is rapid having a half life of 1.8 hours when administered intravenously. Renal dysfunction does not appear to effect the pharmacology of lidocaine. Liver dysfunction may prolong the elimination of lidocaine resulting in delayed recovery from anesthesia. Lidocaine crosses the blood-brain barrier and placental barriers by passive diffusion. It has a pregnancy class B rating (PDR, 1995).

It is virtually impossible to determine the incidence of allergic or toxic reaction to lidocaine because the number of occurrences cannot be equated with the extraordinary number of usages of this commonly-administered local anesthetic. It has been described that anesthetics of the amide class are essentially free of sensitivities. However, lidocaine has a relatively low molecular weight (270.8) and is therefore capable of combining with a protein or higher molecular weight substance forming a haptene. Any haptene has the capability of anitogenicity (Adriana, Coffman, & Naraghi, 1986). Although it is impossible to quantitate adverse reactions to lidocaine, allergic reactions as a result of sensitivity to lidocaine appear to be extremely rare (PDR, 1995).

In a review of 450 cases of adverse reactions to lidocaine submitted to a manufacturer of lidocaine from 1959 to 1975, only 41 of these cases could be classified as allergenic. Approximately one half of the allergenic cases were of the anaphylactic type and ten were due to contact dermatitis. One hundred and seventy five cases were actually symptoms due to overdosage of the drug. Ninety one cases were attributed to psychophysiologic responses such as near-syncope during a dental procedure and one hundred and forty three were symptoms completely unrelated to lidocaine (Adriani et al., 1986).

These same authors reviewed the literature pertaining to adverse reactions to the amide and ester groups of anesthetic agents from 1968 to 1984. During this period, thirty four cases of allergy to either amides or esters were documented.

Of these, 17 resulted from the use of lidocaine and 15 of these were a contact dermatitis reaction.

Lidocaine has been used nearly 50 years in providing effective local anesthesia for dental, medical, and surgical procedures with a very low incidence of side effects. The total incidence of allergic reactions to lidocaine is less than 0.05% (Dickey, 1988). Other types of side effects (slurred speech, drowsiness, hypotension) appear to be dose-dependant and occur only with serum lidocaine levels in the toxic range of 5 to 10 mcg/mL. Serum toxicity levels of lidocaine are unachievable when administering lidocaine locally in the recommended dosages (PDR, 1995). For example, when administering 0.1 ml of a 1% solution of lidocaine intradermally, it is equivalent to administering only 1% of the usual loading dose of lidocaine used in the management of cardiac arrhythmias (Dick et al., 1992).

A Belief That Administration of a Local Anesthetic May Produce More Discomfort Than Venipuncture Itself

There are three methods of administration of lidocaine: injection, iontophoresis, and topical application. Some clinician's believe the administration of these local anesthetics (particularly injection) cause more pain than venipuncture alone.

Some clinicians use lidocaine injected subcutaneously or intradermally over the venipuncture site before intravenous cannulation to eliminate the discomfort associated with this procedure. However, many believe that there is equal or greater discomfort produced by local injection of lidocaine than that produced by intravenous cannulation itself. The following is a review of the literature comparing discomfort produced by local infiltration of lidocaine compared to the discomfort associated with venipuncture.

Intradermal Injection of Lidocaine

In one study, departmental anesthesiologists, believing that injection of local lidocaine before venipuncture was unnecessary if an 18 gauge or smaller cannula were used, cannulated 18, 20, and 22 gauge Venflon intravenous catheters in 60 adult patients about to undergo surgery. The pain scores for these events were compared with pain scores of subcutaneous injection of 1% lidocaine alone, on the opposing hand of these individuals. Findings revealed that IV insertions with cannulas of 18, 20, and 22 gauge were significantly ($p < 0.006$) more painful than subcutaneous injection of 1% lidocaine alone (Harrison, Langham, Bogod, 1992).

Dickey (1988) collected pain scores from 31 adults drawn from a preoperative-day surgery sample where each group was assigned to either: intravenous cannulation with intradermal lidocaine, intravenous cannulation with placebo of sodium chloride, or intravenous cannulation alone. This double-blind study revealed lower pain scores for venipuncture when lidocaine was administered beforehand and greater pain scores for venipuncture without intradermal lidocaine ($p < 0.008$).

A study examining the question, "Does local anesthetic really reduce the pain of venous cannulation in all sizes of IV catheters?" showed that venous cannulation without infiltration of lidocaine, was significantly more painful than venous cannulation with lidocaine for sizes 18, 20, and 22 gauge cannulas (Langham & Harrison, 1992).

It appears that subcutaneous or intradermal infiltration of lidocaine decreases or eliminates discomfort associated with venipuncture. The question, however, is at what expense is this benefit gained? Although used to obtund pain, the infiltration of a local anesthetic may itself produce pain (Morris and Whish, 1984; Morris, McKay, & Mushlin, 1987). The discomfort associated with local infiltration of

anesthetics appears to be less and preferred by patients who undergo intravenous cannulation (Harrison, Langham, & Bogod, 1992).

Optimally, subcutaneous or intradermal infiltration of local anesthetics would be painfree. There have been several approaches in examining ways to reduce or eliminate the discomfort of local infiltration of anesthetics. The following is a review of studies on methods aimed to eliminate the discomfort associated with local infiltration of lidocaine.

A double-blind, controlled study comparing the levels of pain associated with intradermal and subcutaneous injection of five different amide anesthetics showed that etidocaine produced the greatest pain with infiltration while lidocaine and chloroprocaine were rated as the least painful. Bipivacaine and mepivacaine produced relatively intermediate levels of pain. Neither the solution pH nor the pK seemed to influence the degree of discomfort in this study. The lipid solubility of the solution most closely correlated the painfulness of the five anesthetics tested. (Morris et al., 1987).

A similarly-structured study compared the pain experienced with subcutaneous and intradermal infiltration of 1% lidocaine, 1% procaine, and normal saline in 20 adult volunteers. The results revealed that procaine, having the lowest pH of 4.2, inflicted less pain compared with that of lidocaine, having a pH of 5.0. Lidocaine prepared with adrenalin resulted in greatest discomfort while plain lidocaine exerted slightly more discomfort than that of procaine. The differences in levels of pain between all pairs of solutions were statistically significant at $p < 0.05$ or better. (Morris & Whish, 1984).

Several studies demonstrate that adjusting the pH of lidocaine solutions to a near physiologic pH of 7.0 to 7.4 results in less infiltration-associated discomfort (Farley et al., 1994; Christoph et al., 1988; Steinbrook, Hughes, Fanciullo, Manzi, &

Ferrante, 1993; Mader, Playe, & Garb, 1993). Christoph et al. found that in 25 adult volunteers, the level of pain associated with infiltration of amide anesthetics was significantly reduced by buffering the solution to near physiologic pH. The infiltration of 1% lidocaine was 4.5 times more painful than buffered 1% lidocaine and 1% mepivacaine was 5.7 times more uncomfortable than buffered 1% mepivacaine.

The results of this study was bolstered in a double-blind trial with a larger sample size of 184 adults. Lidocaine buffered with sodium bicarbonate caused significantly less pain upon skin infiltration than did 1% lidocaine alone. There were no differences between the two groups with regards to pain attenuated in intravenous cannulation (Steinbrook et al., 1993).

There may be evidence that warming lidocaine solution to body temperature may reduce or eliminate the discomfort associated with subcutaneous or intradermal infiltration of an amide anesthetic. Two studies with sample sizes of 25 each, demonstrated that warming lidocaine to 37 C and 43 C respectively resulted in lower perceived levels of discomfort when compared with infiltration of lidocaine at a room temperature of 21 C (Cragg, Berbaum, & Smith, 1987; Davidson & Boom, 1992). However, when these studies were repeated with larger sample sizes (157 & 40), there was no statistical significance in the pain experienced between those receiving room temperature or body temperature infiltration of lidocaine (Dalton, Sharma, Redwood, Wadsworth, Touquet, 1989; Martin, Jones, Wynn, 1996).

Another approach in reducing discomfort of amide infiltration has been studied. Diluting lidocaine and mepivacaine in balanced salt solution (similar to ophthalmic irrigating solution containing NaCl 0.64%, KCl 0.075%, CaCl 0.03% Na acetate 0.39%, and Nacitrate 0.17%) produced the least amount of discomfort upon infiltration when compared to lidocaine and mepivacaine in commercially prepared

solutions diluted in normal saline. In this study, infiltration discomfort appeared to be directly related to the acidity of the anesthetic, producing the least discomfort when the pH approached an extracellular pH of 7.4 (Farley et al., 1993).

The review of the literature presented demonstrates that (1) infiltration of the local anesthetic lidocaine, when buffered, is significantly less painful than infiltration of nonbuffered lidocaine, and (2) local infiltration of lidocaine reduces or eliminates pain associated with venipuncture.

Iontophoretic Delivery of Lidocaine

Another method designed to deliver local anesthesia is called iontophoresis. Iontophoresis is a painless method of local infiltration of anesthetics, without the use of needles. Iontophoresis is a method of driving a local anesthetic, such as lidocaine, through the skin by applying a small electrical current to the anesthetic solution. The electrical current must have the same polarity as the dissolved molecules of the anesthetic solution. Since like-charges repel each other, the current drives the anesthetic out of solution and into the body surface through sweat glands in the skin (Coats & Lupin, 1995). See figure 4.

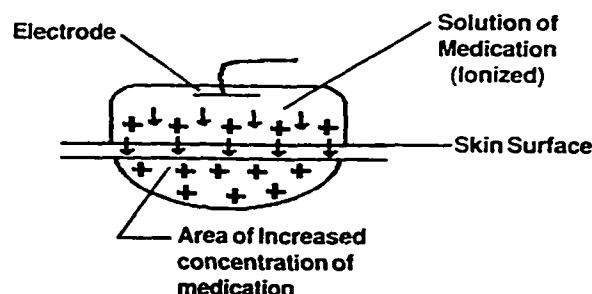


Figure 4. Iontophoresis of positively-charged lidocaine molecules across the skin.

The history of iontophoresis dates back to 1879 when Munck placed strychnine under a positive electrode attached to live rabbit skin and observed that the animal died of strychnine poisoning. In 1989, Morton wrote a book on cataphoresis of ions

into tissues. He placed positively-charged graphite powder under a positive electrode attached to his arm which produced small black spots under his skin (Chein & Banga, 1989). He also studied the anesthetic effects of iontophoresis of cocaine (Gangarosa, 1983).

Contemporary application of iontophoresis began in 1959 when Gibson and Cooke administered pilocarpine by iontophoresis to induce sweating for diagnostic purposes in cystic fibrosis (commonly called the sweat test). Iontophoresis of lidocaine was first used for anesthesia for the hyperemic eardrum (cited in Arvidson, Erroth, Hansby, Lindholm, Whitam-Oleson, 1984).

The principles of iontophoresis are based upon the work of the English chemist, Michael Faraday, who discovered that liquids were conductors of electricity. He discovered that rods, connected to an electrical power source, served as electrodes. Faraday called the rod attached to the positive pole the anode and the rod attached to the negative pole the cathode. He went on to find that when an electric current was placed in certain solutions, chemical decomposition occurred resulting in ions. Positively charged ions were attracted to the negative rod and negatively charged ions were attracted to the positive rod (Fay, 1989). Later it was found that compounds carried their own electrical charges, having a specific conductivity potential or polarity. Polarity is measured as positively or negatively charged. In iontophoresis, positively charged molecules such as lidocaine, will be driven (repelled) across the corpus striatum by way of sweat glands, sebaceous glands, hair follicles, and openings in the junctures of epithelial cells, when a positive electrical current is applied to the solution (Chein, Siddiqui, Shi, Lelawongs, & Liu, 1988).

The only known study of iontophoresis of lidocaine in evaluation for its effectiveness in attenuating pain associated with venipuncture was conducted in 1984. Swedish anesthesiologists recruited 47 regular volunteer blood donors in which 28

persons received lidocaine and 18 received 3% sodium chloride in a double-blind fashion. Twenty one of the 28 receiving lidocaine rated venous cannulation as completely painless whereas 13 of 18 receiving placebo rated their pain as usual. Because a pain scale was not used in this study, a quantitative comparison was not available (Arvidsson, et al., 1984). Four years earlier, Russo, Lipman, Comstock, Page, and Stephen (1980) studied the duration and depth of anesthesia for lidocaine administered by iontophoresis, compared with lidocaine infiltration, and topical lidocaine. Twenty seven subjects each received the three modalities and anesthesia was evaluated by pinprick with a 21 gauge needle every 5 minutes until discomfort was perceived. The mean duration of anesthesia with iontophoresis was 14.5 minutes, with infiltration 22.2 minutes, and swabbing 2.1 minutes. Each subject underwent suturing of the area and reported pain in a categorical fashion of sharp pain, dull pain, and no pain. No participant reported sharp pain and one person reported dull pain.

The anesthetic effectiveness of iontophoresis of lidocaine in dermatological procedures has been studied. Sixty four persons undergoing injections, minor incisions, cautery, laser treatment, excisions, and abrasive treatment were administered 4% lidocaine with epinephrine by iontophoresis. The mean voltage used was 3.4 mA with a mean duration of administration of 8 minutes. Overall, pain relief was rated as excellent by 51% of the patients, adequate by 36%, and inadequate by 14%. Those undergoing excision found iontophoresis to be least effective. Iontophoresis was 80 to 100% effective in injections, abrasions, laser surgery, and cautery. Of 94 iontophoretic administrations, 26 mild adverse effects were noted. Eight were prolonged erythema at the site, in 9 instances, tingling, stinging, or pulling sensation was experienced. A metallic taste was noted by some receiving iontophoresis on the face (Maloney, Bezzant, Stephen, & Petelenz, 1992).

The effectiveness of iontophoresis versus subcutaneous administration of lidocaine has been studied in children. Thirteen pediatric hemodialysis patients, ages ranging from 11 to 19 years, who had been receiving dialysis for at least one year participated. Dialysis requires two independent fistula insertions, therefore each participant served as his own control. Lidocaine 4% was administered with 3mA for 10 minutes before the first fistula cannulation and was again administered by subcutaneous infiltration before the second fistula insertion. The visual analog scale (VAS) was used to measure the child's perceived level of pain during application of both methods of anesthesia. In addition, the study was conducted on 3 separate but sequential dialysis treatments. As was hypothesized, the administration of lidocaine by iontophoresis was rated both least painful and least anxiety-provoking. However by the third session, pain scores for both groups had nearly merged as perceived pain for subcutaneously-administered lidocaine declined over the three trials (Zeltzer, et al., 1991).

The effectiveness of iontophoretic-delivered anesthesia has been compared to topical anesthetic creams in dermatologic practice. A double-blind controlled study was conducted on 10 volunteers between the ages of 26 and 37. Three test sites were placed on each forearm. A topical anesthetic cream or control (moisturizer) was placed on two sites of each arm while the iontophoretic unit was placed on the third test site of each arm where one site delivered 10% lidocaine for an undocumented amount of time, and the other (placebo) unit electrode patch was saturated with 10% of lidocaine as well, however the unit was turned off. Pinprick to the sites were performed at 30 minutes and 60 minutes after the anesthetics were applied. Pain perception was rated in a 6 level categorical fashion. Both the topical anesthetic cream and iontophoresis provided anesthesia greater than the control. Iontophoresis provided greater anesthesia than that of topical anesthetic for both 30 minute

and 60 minute pinpricks ($P = .001$ and $P < 0.05$ respectively). Iontophoresis provided complete anesthesia for 8 of 10 subjects at one hour after application while the topical anesthetic provided complete anesthesia to 1 of 10 at this same interval (Greenbaum & Bernstein, 1994).

Clearly, there have been few studies, with small sample sizes, exploring the efficacy of local anesthesia by iontophoresis. Of those conducted, different parameters have been studied. One explanation for lagging research may be the recognition that application of a direct current to the skin has, on occasion, resulted in minor skin burns or irritation. In the study by Arvidsson, et al., 5 of 47 blood donors developed mild erythema at the site of iontophoresis. One individual from the placebo group developed a burning sensation in this study. Russo et al. (1980) documented sensations of warmth, burning, or cold in 8 and stinging in 6 of 27 participants. Greenbaum et al. (1994) documented no side effects to iontophoresis in 10 subjects. Maloney, et al. (1992) reported erythema in 8 of 26 individuals undergoing iontophoresis. Zeltzer et al. (1991) compared the efficacy of subcutaneous infiltration of lidocaine with iontophoretic delivery of lidocaine in a pediatric dialysis sample. In this trial transient blanching and erythema of application sites occurred with both modalities. Two children were withdrawn from the study after sustaining cutaneous burns during iontophoresis. The authors suggest one explanation for the complications seen in this study may be that the corpus striatum is thinner in children and there may be more porous sweat glands, hair follicles, or epidermal cell junctions. Another explanation may be that uremia in children requiring dialysis predisposes this population to an increased risk of skin injury. There were no episodes of cutaneous burns or injury in the adult populations studied.

When skin injury does occur with iontophoresis it is generally considered to be

as a result of electrolysis of sodium chloride present in both the skin and electrode which forms sodium hydroxide under a positive electrode and hydrochloric acid under a negative electrode. Cathodal (negative electrode) burns tend to be the more serious and studies of these reveal that hydrochloric gas bubbles under the electrode have the effect of separating epidermal cells. When this occurs, there is an increase in flow of current through the epidermis (Leeming, 1970).

In addressing the problem of direct current skin injury as well as skin permeability resistance, a method of transdermal periodic iontotherapeutic system (TPIS) has been developed. With this technique, electrical current is turned on and off systematically during application, having the effect of current pulsations. This allows discharge of electrical current from the skin between pulses, reducing the reaction forming hydrochloric acid. In addition, permeability of drug through skin is maintained at a more constant rate (Chein et al, 1989; Okabe, Yamaguchi, & Kawai, 1987).

Review of the literature reveals that lidocaine delivered by iontophoresis is a viable method of anesthetic delivery. The considerable advantages of iontophoresis in this text is its needlelessness and effectiveness in providing local anesthesia.

Advantages of iontophoresis including other applications have been summarized by Chein, Siddiqui, and Shi, (1990) as follows:

1. avoids the risks and inconvenience of parenteral therapy
2. prevents variation in the absorption and metabolism as seen in oral routes
3. reduces the incidence of over or under dosing by continuous delivery dose
4. permits the use of a drug with a very short half -life
5. permits rapid termination of drug should an intolerance develop
6. permits a means for patient-controlled drug administration
7. iontophoresis of lidocaine is a reimbursable procedure

Potential disadvantages with regards to iontophoresis include:

1. potential for minor skin irritation as well as more serious cutaneous burn (when skin is compromised)
2. the amount of time required for delivery (typically 10 minutes using 3mA)
3. the cost involved (a typical iontophoresis unit costs \$300 and special filling electrodes, called meditrodes, are single-use and obtained only by manufacturers of these devices)

Topical Eutectic Lidocaine

The third method of administering a local anesthetic is topical application. In 1981, The Swedish scientist, Fredrick Broberg, discovered that when crystalline amide-type anesthetics lidocaine and prilocaine were mixed, they became an oily fluid. In 1983, The topical anesthetic cream (EMLA) was approved for medical use. Over the last decade, topical anesthetic creams have become increasingly popular for attenuating pain associated with venipuncture as well as other minor dermatological, otological, gynecological, and urological procedures (Lee & Rubin, 1993).

EMLA is an acronym for eutectic mixture of local anesthetics. The term eutectic refers to the pharmacokinetics whereby the melting point of two anesthetics is lower when they are combined than when alone. Lidocaine and prilocaine are active amide-type anesthetics which when alone are crystals, but when combined, form an oil at 25 C which is then emulsified in water. Each gram of EMLA 5% cream contains lidocaine 25 mg., prilocaine 25 mg., polyoxyethylene ester 19 mg. (emulsifier), carboxyethylene 10 mg. (thickener), sodium hydroxide (adjusts pH to 9), and purified water (Astra Pharmaceutical, 1996). See figure 5.

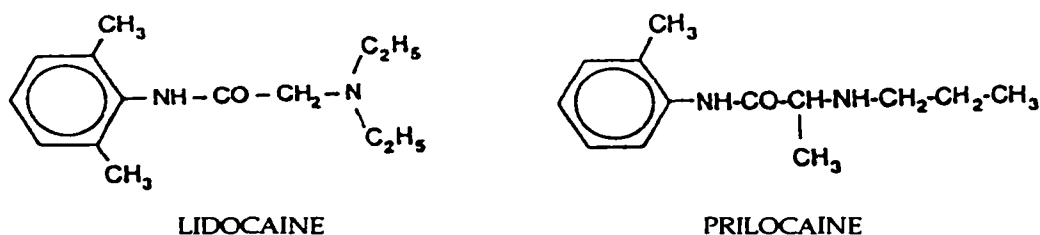


Figure 5. EMLA cream contains both lidocaine and prilocaine in equal proportion.

Passive diffusion of drug through the skin is called transdermal drug delivery (TDD). TDD has been applied to several commonly-prescribed medications including estadiol-releasing, nitroglycerin-releasing, clonidine-releasing, and scopolamine-releasing systems (Chein, et al., 1989). EMLA cream also relies on the pharmacophysiology of TDD. Skin consists of the epidermis, dermis, and subcutaneous tissue. The epidermis is comprised of five layers in which the outermost layer (stratum corneum) is about 20% water and the innermost layer (stratum germinativum) is 70% water. This is important in that the high concentration of purified water in the emulsion (92%) assists penetration of the drug through the relatively dry stratum corneum (PDR, 1996). As in lidocaine solution, there are charged and uncharged portions of EMLA emulsion whereby the uncharged form is responsible for penetration through the skin and the charged portion is responsible for blockade of neurotransmission (Buckley & Benfield, 1993). Unlike iontophoresis technology, TDD systems do not create greater permeability by altering the organization of epidermal cells. TDD is based upon passive diffusion relying on the 40 to 70 hair follicles and 200 to 250 sweat ducts contained on every square centimeter of normal skin (Chein, et al., 1989).

Astra, the pharmaceutical manufacturer of EMLA, recommends application of a thick layer of the cream, 1 - 2 gram/ 10 cm (2 inches x 2 inches) on intact skin at the site of venipuncture. The area is then covered with an occlusive dressing much like Tegaderm. After one hour, the dressing is removed, the EMLA cream wiped off,

and the skin is then prepared as usual for venipuncture (Astra Pharmaceuticals, 1996).

Lidocaine is almost entirely metabolized by the liver and prilocaine is metabolized equally by liver and kidneys. Systemic absorption of eutectic lidocaine/prilocaine cream has been studied and appears to be minuscule. In general, maximum serum plasma levels appear to be 10 to 100 fold less than concentrations considered to be toxic for these drugs (Astra Pharmaceuticals; Juhlin et al., 1989; Evers et al., 1985). One study evaluating absorption levels of lidocaine and prilocaine revealed that when 60 grams is applied to 400cm of normal skin for 3 hours, serum lidocaine was measured to be 1/24 of serum toxic level for lidocaine and prilocaine was measured to be 1/36 the serum toxic level known for prilocaine (Astra Pharmaceutical, 1996). It has been found that the rate of absorption (TTD) of EMLA cream into subcutaneous tissue as well as vasculature, may vary according to the anatomical location the cream is applied and the condition of the skin. Juhlin et al. found that EMLA is absorbed more rapidly through facial skin than skin of the forearm. When EMLA 5% was applied 10 gram/100cm to facial skin, mean plasma lidocaine and prilocaine levels peaked 2 hours after application which were 150 mcg/L and 58 mcg/L respectively. When the same dosage was applied to the forearm, peak serum plasma level for lidocaine was only 18 ug/L 5 hours after application and prilocaine was undetectable in serum plasma (Juhlin & Evers, 1990).

It is recommended that EMLA cream be applied to intact, healthy skin. When EMLA was applied to psoriatic lesions of 10 subjects, serum plasma lidocaine levels one hour later ranged from 16 to 450 mcg/L. Prilocaine was detectable in 7 of 10 individuals and serum concentration levels in these ranged from 20 to 190 mcg/L. It appears there is greater variability in absorption and serum concentration levels in both drugs when skin is compromised (Juhlin, Haglund, & Evers, 1989).

Absorption levels of EMLA cream have been studied in children. Ten grams of lidocaine/prilocaine cream were applied to 10 sites on 10 children aged 2 and 3 years. Between 2 and 3 hours after application, serum plasma concentrations for lidocaine and prilocaine ranged from 92 to 315 mcg/L and 45 to 215 mcg/L respectively (Haugstvedt, Friman, & Danielson, 1990). The recommended doses by Astra Pharmaceutical is 1-2 grams/10cm for a duration of no longer than 2 hours. EMLA cream is not recommended for infants younger than 3 months of age.

EMLA cream demonstrated no teratogenic effects in pregnant rats when applied 22 times the usual dose for humans (Astra Pharmaceuticals, 1996). However, no studies have been conducted on pregnant women, therefore, the manufacturer recommends use of EMLA cream in pregnant women only if absolutely needed.

Lidocaine/prilocaine eutectic mixture appears to be well-tolerated. Similar to its parenteral counterpart, topical lidocaine appears to cause rare sensitivities or allergic reactions. Likewise, prilocaine is associated with rare side effects.

The following localized reactions were seen in 1,500 patients receiving EMLA cream: blanching of skin 37%, erythema 30%, edema 6%, pruritis 2%, and rash in less than 1% (Astra Pharmaceutical, 1996).

Bjerring et al. (1989) studied the peripherovascular effects of EMLA in 9 healthy volunteers. Initially, blanching and pallor were observed at the site of application at 30 and 60 minute intervals, followed by erythema at 2 hours from application. This may reflect an initial vasoconstriction followed by vasodilation. It is interesting that placebo cream demonstrated similar findings. It is thought that the occlusive dressing used in this study may have played a role in the vascular response observed. However, when this study was repeated with a sample size of 50 healthy volunteers, blanching was seen in 66% of the treated group and in only 6% of the placebo group. Erythema occurred in 34% of those receiving EMLA cream and 2%

in those receiving placebo cream (Villada, Zetlaoui, & Revuz, 1990).

In all clinical trials, the most common side effects, blanching and erythema at the site of application, were transient lasting less than 2 hours. EMLA cream is so well tolerated it has been described as producing no interference with wheal and flare responses in intradermal skin testing. In this study, 36 of 40 children received complete dermal anesthesia during skin testing (Wolf, Shier, Lampl, & Schwartz, 1994).

There has been a single case of methemoglobinemia in a 3 month old infant who received 5 grams of EMLA cream to the back of both hands and cubital regions for 5 hours. This infant was also taking sulfamethoxazole 80 mg daily for a urinary tract infection. For this reason, Astra Pharmaceuticals warns against the use of EMLA cream in infants and children receiving sulfa drugs or persons having glucose-6-phosphate dehydrogenase deficiency (G6PD). Hemolytic anemias have been known to occur when persons having G6PD are given sulfa, macrodantin, acetaminophen, nitrates, dilantin, quinine, dapsone, and phenobarbitol.

The effectiveness of EMLA as a topical anesthetic has been well documented in a growing body of clinical trials. Most of the clinical data on EMLA cream have been generated from pediatric populations. In these trials, pain was quantitated by means of a verbal rating scale or visual analog scale (VAS). Participants in these studies were age three months to seventeen years. All trials were double-blind and placebo controlled. In all studies involving children undergoing venipuncture, EMLA cream provided significantly greater pain relief than placebo (Clark & Radford, 1986; Cooper et al. 1987; Joyce et al. 1993; Kurien et al. 1985; Moller, 1985; Robieux et al. 1991).

Application of eutectic lidocaine/prilocaine cream under an occlusive dressing can be inconvenient and the precise dosage applied may be questionable. To

improve application, a prepackaged, single use, patch delivery system has been developed whereby each patch delivers 1 g of 5% eutectic lidocaine/prilocaine. Clinical trials thus far (Stewart et al. 1992, Robieux et al. 1992, Chang, et al. 1993) have revealed the EMLA patch to afford the same effectiveness and tolerability as a local anesthetic in venipuncture, as provided by EMLA cream.

EMLA cream has been studied in adults undergoing venipuncture. Nott and Peacock (1990) found there to be significantly less pain ($p < 0.005$) with venipuncture in 120 adults when EMLA cream was applied for 60 minutes than with placebo for the same time period. In a double blind trial of 100 adults undergoing venipuncture, both pain relief and ease of venipuncture were found to be significantly greater ($p < 0.001$) after 60 minute application, when comparing EMLA cream to placebo (Gunawardene & Davenport, 1990). Maddi, Horrow, Conception, and Murray (1990) investigated the most efficacious application interval in 75 adults undergoing venipuncture. They found 45 to 60 minutes to be the minimal effective application time for EMLA cream in achieving significant anesthesia for venipuncture.

Assessment of Pain

Assessment and measurement of pain is complex. Pain may be approached singularly, conformed to a point or a number on a scale, or pain can be considered completely individualistic and unmeasurable. As best described by McCaffery (1972) 'pain is whatever the experiencing person says it is, and exists whenever he says it does' (cited in Latham, 1994).

It has been well-documented in the literature that stress and illness can heighten the perception of pain. It has also been well documented that pre-procedure education reduce both stress and discomfort associated with hospital procedures.

There appear to be no clinical investigations assessing the psychosocial influences with regards to venipuncture-associated pain. Although not directly measured, the Zeltzer study (1989) hinted to operational self efficacy as pain scores for infiltration of lidocaine declined with each additional intradermal injection.

Summary

The literature reviewed appears to overwhelmingly support the use of lidocaine as a safe and effective local anesthetic reducing or eliminating the pain of venipuncture. However, there exist limitations in the clinical trials presented. There are few clinical trials with large numbers of participants. Studies tended to have enrollees as few as 7 up to 184. There is a lack of homogeneity among the trials as different variables have been studied (eg. duration of anesthesia, depth of anesthesia, degree of anesthesia). Earlier study designs omitted placebo and double blinding safeguards. Many different pain assessment tools have been used in the past with the Visual Analog Scale emerging as the pain assessment tool of choice over the last decade.

The review of the literature identifies several key areas for the current study to address. Among clinicians, there has yet to emerge a consensus as whether or not to administer a local anesthetic prior to venipuncture. An article published in the American Journal of Nursing "How to Boost the Odds of a Painless IV Start," resulted in both "ye" and "ne" responses in editorials published by the journal. With an arsenal of safe and effective pain-relieving measures there lacks an appreciation for which delivery measure is most effective, most efficient, best tolerated, and preferred by recipients. If a specific pain-relieving measure can be repeatedly identified as superior when compared to others, there may be a greater likeliness for clinicians to adopt this important practice. Ideally, pain-relieving

measures will someday be viewed of as a menu to be selected from, best suiting the individual recipient and the situation.

Research Hypotheses

The hypotheses tested in this study were: (1) anesthetic-associated pain will be rated significantly lower when compared to venipuncture pain, (2) venipuncture-associated pain will be rated significantly lower in all three treatment groups when compared to placebo, and (3) iontophoretically-delivered lidocaine will emerge as a preference among the three treatments.

Three mutually exclusive parts of the study were analyzed: (1) variances between all subjects, (2) variances due to treatments, and (3) variances within the subjects' response to the treatments. In addition, results of the questionnaire show what percentage of participants preferred each treatment as well as preferences for their children.

Definition of Terms

Intradermal Injection is infiltration into subcutaneous tissue just below the skin. Small gauge needles (27 g) are used with tuberculin or insulin syringes to deliver 0.5 ml of 1% lidocaine.

Iontophoresis is a needleless infiltration technique whereby a 2% lidocaine solution is propelled through the skin via sweat ducts, hair follicles, and epithelial cell junctures, by a tiny electrical current from a battery-powered unit, providing local anesthesia to a skin depth of 6 mm when using 3.5 mA current for 7 minutes.

Eutectic Lidocaine/Prilocaine Cream is an emulsion containing 25 mg of lidocaine and 25 mg of prilocaine as well as Arlatone (an emulsifier), a thickener and distilled water, when applied topically, under an occlusive dressing, for one hour, provides

local anesthesia to a skin depth of 2 mm.

Pain is the subjective perception of sensation(s) experienced at the moment of each treatment and at the moment of venipuncture. Each participant will distill this experience onto a mark or point placed along a 100 mm visual analog pain scale.

CHAPTER THREE

METHODOLOGY

Study Design

A quasi-experimental, double blinded, design was used to examine the relationship comparing the tolerability of three delivery methods for local infiltration of lidocaine along with the effectiveness in attenuating venipuncture pain following each method of anesthesia. The study enrolled participants who served as their own control. Each participant received three different methods of local delivery of lidocaine whereby each of the three treatments (lidocaine by intradermal injection, lidocaine by iontophoresis, and topical lidocaine/prilocaine cream) was administered approximately one week apart. The one-week interval between treatments was determined sufficient time to observe for local reactions and to allow for recovery of the treated area before subsequent treatments.

Sample and Setting

Twenty-two healthy adult medical and paramedical employees met eligibility and volunteered to participate in this study. A volunteer sample of healthy individuals was important in delineating out possible threats to internal and external validity such as emotional influences associated with hospitalization, surgery, and illness with regards to the perception of pain. It is acknowledged that medical and paramedical staff who volunteered for participation in this study may possess a higher threshold for pain by virtue of their informed consent for undergoing multiple venipunctures. It was also recognized that medical and paramedical volunteers may be more comfortable undergoing invasive-type procedures when

compared to a randomized sample. Therefore, the results of this study may not be assuredly generalized to the general population. These limitations, however, would be expected to bias the results conservatively with pain scores tending lower in this sample when compared to pain scores obtained from a randomized sample or from an inpatient hospital sample.

Eligibility criteria:

1. English speaking of age 21 to 55 years
2. Absence of major or chronic illness
3. Specifically, absence of cardiac, liver, kidney disease, or G-6-P deficiency
4. No known allergy or sensitivity to lidocaine
5. No known allergy or sensitivity to prilocaine
6. Taking no medications with the exception of nutritional supplements
7. Specifically, taking no sulfa drugs
8. Non-pregnant
9. No unusual skin disorders
10. No pacemaker or cardiac implantable defibrillator
11. Absence of emotional or psychological disorder(s)
12. Provide informed consent

Instruments

It is acknowledged that the experience of pain is as individual and unique as each human being. Given the complexity of pain, there can be no perfect assessment tool. However, if the effectiveness of pain-reducing interventions proposed in this study are to be evaluated, differences in pain must be measured. With an

appreciation for this, the study used a horizontal visual analog scale with a length of 100 mm to measure the level of pain experienced with each administration of lidocaine and with each venipuncture (See Appendix A).

The visual analog scale (VAS) is a tool frequently used in the measurement of pain. The tool was first introduced by Keele in 1948 when he placed the words:

none—slight—moderate—severe—agonizing

in this fashion, and asked individuals to rate their pain along this verbal descriptor scale (Latham, 1994). The tool has evolved to a simple line, usually 100 mm in length, with perpendicular lines at each end to signify extremes of the phenomena under study. Verbal prompting can be minimal (no pain) just left of the line and (worst pain I can imagine) to the right of the line. Or there may be verbal indicators spanning the entire length of the line much like the example above. Individuals are asked to place a single mark along the line exemplifying the level of pain they are experiencing. This visualization becomes quantifiable when the distance between the left margin of the line and the subject's mark along the line is measured, yielding a numerical value in millimeter units.

Construct validity (cited in Gift, 1989; Wewers & Lowe, 1990) has been established for the VAS. Reliability for the VAS has been as high as .95 to .99 in assessing pain to as low as .41 to .91 in assessment of mood. Reliability is greatest when measuring intersubjectly and somewhat lower when sample groups are compared. Reliability remains high (.95) for up to 24 hours between pretest and posttest for pain (cited in Wewers & Lowe, 1990).

In this study, each participant was asked to mark the level of their pain after each treatment and after each venipuncture. Participants were in a seated position in a well-lighted area. Because there was a one week interval between retests, partic-

ipants were allowed to view their VAS scores from prior sessions as Scott and Huskisson (1979) found that patients tended to overestimate the current pain experience when previous scores were unavailable.

The Visual Analog Scales were collected from participants in a manner to ensure complete anonymity from the researcher. The VAS were numbered from 01 to 22 and participants were asked to memorize the number on their VAS. The forms were collected by the registered nurse administering the treatments. On subsequent treatment sessions, participants collected their numbered VAS from a pile. Following the third session, the VAS were collected by the IV nurse and returned to the researcher. These measures were intended to maximize internal reliability.

Procedures for Data Collection

Eligible recruitments for this study received an explanation of the purpose of the study and a thorough explanation as to the methodology, timeliness, and potential risks of the study outlined throughout the written consent form (See Appendix B). The consent form also informed the candidates that participation was completely voluntary and participants could withdraw from the study at any time. Questions about the methodology or risks of the study were elicited from each candidate. Once the individual verbalized understanding of the study, he or she was given the opportunity to voluntarily participate in the study by signing the written consent.

Meeting # 1: Intradermal Injection with Lidocaine Followed by Venipuncture

Approximately two hours before administration, three milliliters of 8.4% sodium bicarbonate (NaHCO_3) was added to a 30 cc multidose vial of 1% lidocaine raising the pH of lidocaine from a range of 5 to 6 to approximately 7.41 as measured

by a Corning pH Meter Model 345. Neither the administrator nor recipient was aware of whether the vial contained buffered lidocaine or placebo of 0.9 sterile normal saline as vials were labeled "solution 1" and "solution 2".

The antecubital aspect of one arm was cleansed with 70% alcohol. A tuberculin syringe with a 27 gauge needle was used to inject a solution 0.5 ml of 1% lidocaine and 0.1 meq NaHCO_3 intradermally at a 5 degree angle to the skin, with bevel up, over 3 to 5 seconds, forming a wheal over the anticipated venipuncture sight. Cannulation of the vein using a Insyte 20 gauge intravenous catheter was then carried out. Immediately following intradermal injection and again after IV cannulation, participants were asked to evaluate the intensity of pain associated with each procedure by placing a mark along a 100 mm VAS.

On the antecubital aspect of the opposing arm, the procedure was repeated as above, whereby a 27 gauge syringe was used to administer 0.5 ml of unpreserved sterile sodium chloride intradermally and cannulation of the vein using an Insyte 20 gauge catheter was carried out. Following each procedure, participants were asked to measure the intensity of pain associated with each procedure by placing a mark along a 100 mm VAS.

The intravenous catheter was promptly removed, light pressure over the sight maintained for 10 seconds or until bleeding had stopped, and a bandaid applied with instructions for removal in two hours.

Participants were observed for symptoms of allergic reaction for 30 minutes following termination of the last IV catheter. Participants were reminded to contact the researcher if symptoms such as redness, swelling, or pruritis occur at the site(s). The researcher attempted to contact each participant by telephone approximately 24 hours following treatment to evaluate for side effects.

Meeting #2: Iontophoresis of Lidocaine Followed by Venipuncture

The iontophoretic unit used in this study was the Needle Buster Model NB-1 manufactured by Life-Tech. Inc. located in Houston, Texas. Iontophoresis was applied according to the manufacturer's guidelines. Approximately two minutes prior to administration, each Life-Tech Inc. Meditrode was filled with 2 cc solution of 2% lidocaine. For the opposing arm treated with placebo, approximately two minutes before administration, each Meditrode was filled with 2 cc of sterile, unpreserved sodium chloride. The containers were labeled "solution 1" and "solution 2" to ensure blinding of the administrator and the recipients.

The antecubital aspect of one arm was wiped clean with sterile 4 x 4 gauze. The Life-Tech Inc. Meditrode labeled "solution 1" was placed upon the prepared area. An indifferent electrode was affixed nearby. The unit was connected to the electrodes and a current of 3.0 mA was applied for 8.3 minutes for 9 individuals, 7.5 minutes for 2 individuals, and 7.0 minutes for one individual. Each recipient was asked if he or she was able to perceive the current. If so, the current was titrated downward until there was no perception of current. One recipient was able to perceive current of 3.0 mA. The mA was gradually decreased to 1.5 mA and the unit was shut off at 7 minutes. The skin was reexamined for breaks or other imperfections but none were found.

Following treatment, the skin was cleansed with 70% alcohol and cannulation of the vein using a 20 gauge Insyte catheter was carried out. Immediately following iontophoresis of the solution, and again after venipuncture, participants were asked to evaluate the intensity of pain associated with each procedure by placing a mark along a 100 mm VAS.

On the opposing arm, the procedure was repeated as above whereby the

Meditrode labeled "solution 2" was applied. The iontophoresis unit remained in the "off" position for 8.3 minutes. The skin was cleansed with 70% alcohol and cannulation of the vein using a 20 gauge Insyte catheter was carried out. Immediately following iontophoresis, and again after venipuncture, participants were asked to evaluate the intensity of pain associated with each procedure by placing mark along a 100 mm VAS.

The intravenous catheter was promptly removed, light pressure over the site was maintained for 10 seconds or until bleeding had stopped, and a bandaid applied with instructions to remove in 2 hours.

Participants were observed for symptoms of allergic reaction for 30 minutes following termination of the last IV catheter. Participants were reminded to contact the researcher if symptoms such as blanching, redness, swelling, or pruritis occur at the site(s). The researcher attempted to contact the participants by telephone approximately 24 hours following treatment to evaluate for side effects.

Meeting #3: Topical Application of EMLA Cream

The eutectic lidocaine/prilocaine cream used in this study was EMLA manufactured by ASTRA Pharmaceuticals located in Westborough, Maryland. EMLA cream was applied according to the manufacturer's instructions (See Appendix D).

Both the administrator and recipient were unaware of the cream used as one container was labeled "cream 1" and another container labeled "cream 2". An odorless, perfume-free hand lotion, having the same consistency and color as EMLA cream, was used for placebo.

2.5 grams of cream labeled "cream 1" was applied to 2 inches by 2 inches of skin of the antecubital aspect of one arm. An occlusive Tegaderm dressing was applied

over the cream. After the cream had been maintained for 60 minutes, the occlusive dressing was removed and the skin wiped clean of the cream with a sterile 4 by 4 gauze.

Following treatment, the skin was cleansed with 70% alcohol and cannulation of the vein using a 20 gauge Insite catheter was carried out. Immediately following removal of the Tegaderm dressing and again after venipuncture, participants were asked to evaluate the intensity of pain associated with each procedure by placing a mark along a 100 mm VAS.

On the opposing arm, the procedure was repeated as above whereby cream labeled "cream 2" was applied, Tegaderm occlusive dressing applied, and the cream then removed after 60 minutes with a 4 inch by 4 inch sterile gauze. Following treatment, the skin was cleansed with 70% alcohol and cannulation of the vein, using a 20 gauge Insite catheter was carried out. Immediately following removal of the Tegaderm dressing and again after venipuncture, participants were asked to evaluate the intensity of pain associated with each procedure by placing a mark along a 100 mm VAS.

The intravenous catheter was promptly removed, light pressure was maintained for 10 seconds or until the bleeding had stopped, and a bandaid applied with instructions to remove in 2 hours.

Participants were observed for symptoms of allergic reaction for 30 minutes following removal of the last IV catheter. Participants were reminded to contact the researcher if symptoms such as redness, swelling, or pruritis occur at the site(s). The researcher attempted to contact each participant by telephone approximately 24 hours following treatment to evaluate for side effects.

Human Subject Consideration

Before data collection began, the proposal was submitted to Grand Valley State University Human Research Review Committee and to The Chief Executive Officer and a committee of three physicians of the Milliken Medical Group. Each gave permission to proceed with this clinical trial.

Expected risks to the participants in this study were anticipated to be extremely small if any. There was a 0.5% risk for an allergic reaction to lidocaine or prilocaine. There was an estimated 33% risk for transient blanching or erythema at the treatment site(s) lasting less than 24 hours. There may be bruising of the venipuncture site(s).

It was unknown whether participants would develop psychological or emotional anxiety related to multiple venipunctures. However, there have been no such indications in the literature prompting issuance. The time required by the participants in this study may have been an inconvenience. There were no expected benefits to the participants of this study. Following completion of the study, one participant confided she had had a "terrible fear" of needles resulting from a "bad experience with an IV" she had received at the age of sixteen. This participant stated enrollment in this study was an attempt to "beat the fear" which she claimed was the case.

CHAPTER FOUR

RESULTS

Twenty subjects underwent two treatment sessions and 12 of those participants underwent three treatment sessions. A total of 208 observations were measured. In treatment 1, four pain scores were collected from each of 20 subjects on June 6, 1997 for: (a) intradermal injection of lidocaine, (b) venipuncture following intradermal injection of lidocaine (c) intradermal injection of sodium chloride, (d) venipuncture following intradermal injection of sodium chloride. In treatment 2, four pain scores were collected from each of twelve subjects on June 13, 1997 for: (a) iontophoretic administration of lidocaine, (b) venipuncture following iontophoretic delivery of lidocaine, (c) placebo for iontophoretic delivery of lidocaine, (d) venipuncture following placebo for iontophoretic delivery of lidocaine. In treatment 3, four pain scores were collected from each of 20 subjects on June 20, 1997 for: (a) topical EMLA cream, (b) venipuncture following topical EMLA cream, (c) topical hand lotion, (d) venipuncture following topical hand lotion. The observations for each treatment and their placebo was measured using a 100 millimeter Visual Analog Scale. Data in this study are considered interval level.

Following the first two treatments with iontophoresis and subsequent venipunctures, it became apparent that these participants measured pain scores for venipuncture following iontophoresis higher than was to be expected and in these cases pain scores for venipuncture were similar to pain scores for venipuncture following placebo. In a discussion with a technical support representative for Life-Tech., Inc., it was advised to increase the application time to 15 minutes starting at 2 mAmps and titrating the current upward. The manufacturer's guidelines recommend applying 2 to 4 mAmps for 7.5 to 15 minutes for the size meditrode used in this

study. However, some participants, mostly physicians behind in their schedule that day, were unable or unwilling to allow for the planned iontophoresis of 7.5 minutes and asked to forego this session. Therefore, only 12 of the 20 participants underwent this treatment session. Based on tolerability of iontophoresis, nine individuals received 3 mAmps current for 8.3 minutes and two individuals received 3 mAmps current for 7.5 minutes. One individual received 7.0 minutes of treatment requiring titration of current downward to 1.5 mAmps. The mean treatment time for the group was 8.07 minutes. The mean current for the group was 2.9 mAmps.

The observations were plotted and found not to be normally distributed. Nonparametric statistics were applied in the analysis of the observations. The Friedman statistic (nonparametric) was used to measure variances within and between all three treatment groups for the 12 participants. The Friedman test derives results within 95% accuracy of its parametric equivalent, Repeated Measures Analysis of Variance (Glantz, 1992). The Wilcoxin Signed Rank test (nonparametric) was used in examining the 20 participants undergoing only two of the three treatments (this population arose when 8 of 20 participants did not undergo treatment #2 Iontophoresis of Lidocaine). In this case, pairwise comparisons were made between treatment groups #1 (Injection of Lidocaine) and #3 (EMLA Cream).

A Bonferroni Inequality was applied in the analysis to correct for multiple testing on two separate and small sets of data: (1) comparisons of pain levels experienced with each different method for delivery of lidocaine, and (2) comparisons of pain levels experienced with venipuncture following each of the three treatments. After Bonferroni correction, a probability of 0.02 or less was determined to be "significant" (sufficiently low to reject the null hypothesis that none of the three treatments will have an effect on venipuncture pain).

Of the 22 volunteers, 20 participants completed the study. One participant was dismissed from the study when she demonstrated symptoms of distress upon receiving the first treatment. These symptoms included sudden and new verbalization of apprehension regarding needle puncture, expressed feelings of warmth, mild pallor and diaphoresis. These symptoms were brief and without sequelae. Another volunteer was dismissed from the study when she verbalized having had a local reaction to an immunization in the remote past.

Of the 20 participants completing the study, 50% (n=10) were females, 40% (n=8) were males, and 10% (n=2) were unidentified. Their ages ranged from 24 to 55 years with a mean age of 39.4 years. All participants were Caucasian. All individuals were medical or paramedical employees volunteering participation during their normal workday in the conference/lunch room of the medical building in which they work.

Hypotheses Testing

The hypotheses tested in this study were: (1) anesthetic-associated pain will be rated significantly lower when compared to venipuncture-associated pain, and (2) venipuncture-associated pain will be rated significantly lower in all three treatment groups when compared to placebo, and (3) iontophoretically-delivered lidocaine will emerge as a preference among the three treatments.

Comparison of Pain Between Local Anesthetic and Placebo

Comparison of Intradermal Injection of Lidocaine with Placebo

For intradermal injection of buffered lidocaine, pain scores ranged from 0.0mm to 39.0mm with a mean pain score of 12.0mm. The standard deviation was 11.4mm. For intradermal injection of normal saline, pain scores ranged from 3.0mm to

45.0mm with a mean pain score of 20.0mm. The standard deviation was 12.5mm. There was a significant difference in perceived pain between intradermal injection of lidocaine and intradermal injection of normal saline with injection of buffered lidocaine resulting in significantly lower pain scores ($p = .0021$).

Comparison of Iontophoretic Delivery of Lidocaine with Placebo

For iontophoretic delivery of lidocaine, pain scores ranged from 0.0mm to 41.0mm with a mean pain score of 6.33mm. The standard deviation was 12.4mm. For iontophoretic delivery of normal saline, pain scores ranged from 0.0mm to 6.0mm with a mean pain score of 0.8. The standard deviation was 1.8mm. There was no significant difference in perceived pain between iontophoresis of lidocaine and iontophoresis of placebo ($p = .110$).

Comparison of EMLA Cream With Placebo

For application of topical EMLA cream, pain scores ranged from 0.0mm to 17.0mm with a mean pain level of 1.5mm. The standard deviation was 4.0mm. For application of EMLA placebo, pain levels ranged from 0.0mm to 52.0mm with a mean of 3.0mm. There was no significant difference in perceived pain between the application of topical EMLA cream and the application hand lotion ($p = .68$).

Comparison of Pain Between Anesthetics

Comparison of Injection With Iontophoresis

When comparing the pain experienced with injection of buffered lidocaine with iontophoresis of lidocaine $p = .80$. Therefore, there was no significant difference in pain perceived between the two delivery techniques. The mean pain

score for injection of lidocaine was 12.0mm and the mean pain score for iontophoresis of lidocaine was 6.3mm.

Comparison of Injection With EMLA Cream

When comparing the pain experienced with injection of buffered lidocaine with topical EMLA cream $p = .018$. Therefore, there was a significant difference in pain perceived between injection of lidocaine and topical EMLA cream. The mean pain level for injection of lidocaine was 12.0mm and the mean pain level for EMLA cream was 1.5mm.

Comparison of Iontophoresis With EMLA Cream

When comparing the pain experienced with iontophoresis of lidocaine to that experienced with EMLA cream $p = .034$. Therefore, there was no significant difference in the pain perceived between these anesthetics. Mean pain levels for iontophoresis of lidocaine was 6.3mm and the mean level for EMLA cream was 1.5mm.

Effects of Local Anesthesia Upon Venipuncture Pain

Pain scores for venipuncture following all treatments were significantly lower than pain scores for venipuncture following placebo. See summary of pain scores in Table 1 on page 49.

Venipuncture Pain After Injection With Lidocaine

Pain scores for venipuncture following intradermal injection of lidocaine ranged from 0.0mm to 24.0mm with a mean pain level of 7.1mm. The standard deviation was 7.1mm. Pain scores for venipuncture following injection with normal saline ranged from 6.0mm to 53.0mm with a mean pain level of 25.0mm. The mean level of venipuncture pain using placebo is more than thrice that of

venipuncture pain with anesthesia. When comparing venipuncture pain with injected lidocaine to venipuncture pain with injected placebo, $p = .001$. Therefore, there is significantly less discomfort when venipuncture is pretreated with injected lidocaine when compared to venipuncture pretreated with placebo.

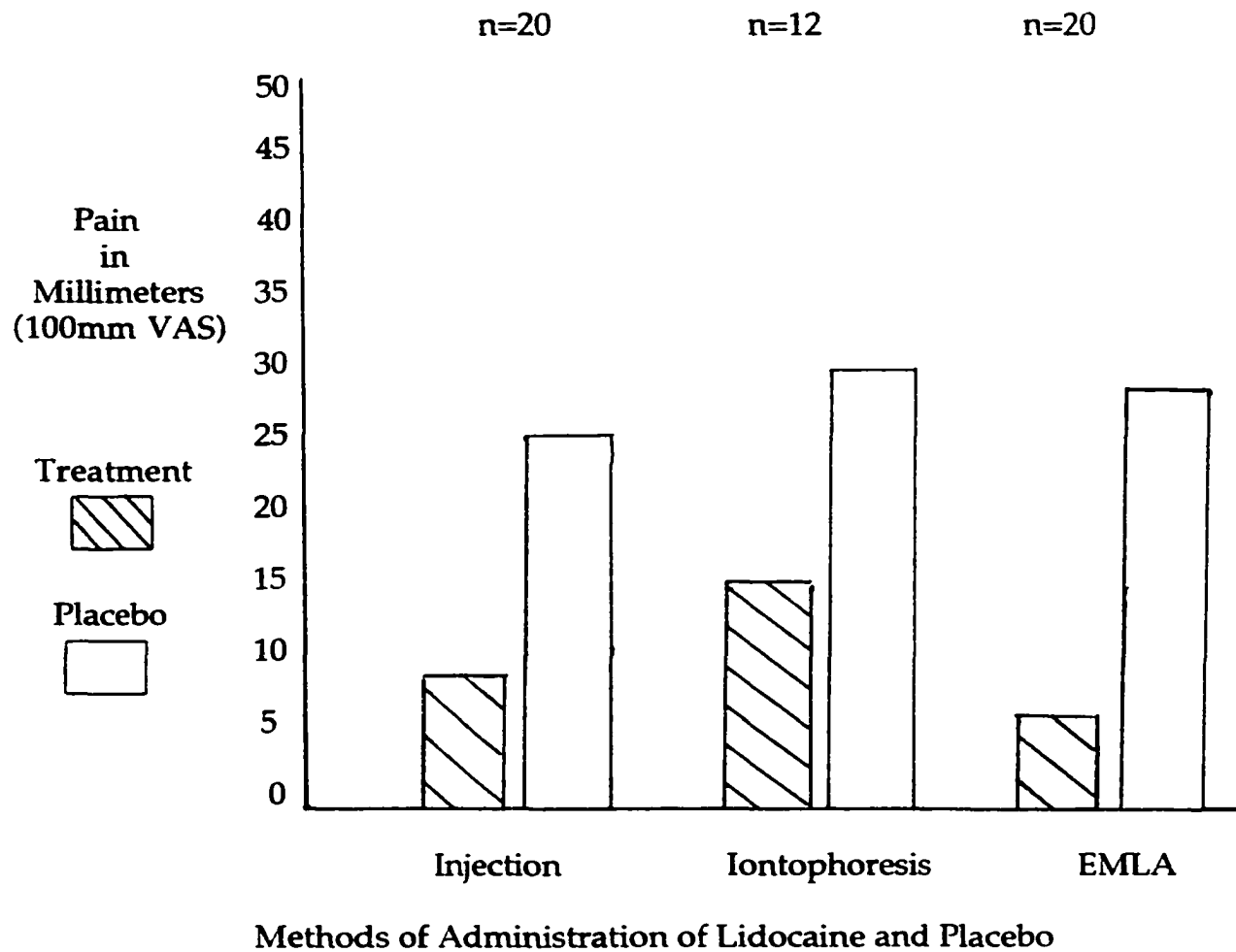
Venipuncture Pain After Iontophoresis of Lidocaine

Pain scores for venipuncture following iontophoresis of lidocaine ranged from 5.0mm to 38.0mm with a mean pain level of 15.4mm. The standard deviation was 10.0mm. Pain scores for venipuncture following iontophoresis of placebo ranged from 3.0mm to 61mm with a mean pain level of 29.5mm. The standard deviation was 19.6mm. The mean pain score for venipuncture without iontophoresis was twice the mean pain score with anesthesia by iontophoresis. In comparing venipuncture pain with and without iontophoresis, $p = .0053$. Therefore, there is a significant reduction in venipuncture pain with iontophoresis of lidocaine when compared to venipuncture pain following treatment with placebo.

Venipuncture Pain After Application of EMLA Cream

Pain scores for venipuncture following EMLA cream ranged from 0.0mm to 60.0mm with a mean pain level of 6.3mm. The standard deviation was 6.7mm. Pain scores for venipuncture following application of placebo ranged from 4.0mm to 60.0mm with a mean pain level of 27.3mm. The mean pain score for venipuncture following pretreatment with hand lotion was over quadruple that of the mean pain score when EMLA cream was used. In comparing venipuncture pain between the use of EMLA and placebo, $p = .0001$. Therefore, there is a significant reduction in pain experienced with venipuncture pretreated with EMLA cream when compared to venipuncture pretreated with placebo.

Table 1. The Influence of Treatments Upon Mean Venipuncture Pain Levels



Comparison of Venipuncture Pain Between Anesthetics

Comparison of Injection With Iontophoresis

When comparing mean levels of pain for venipuncture following injection of lidocaine and mean pain levels for venipuncture following iontophoresis of lidocaine $p = .0422$. Therefore, there is no significant difference in venipuncture pain whether there was pretreatment with injection or iontophoresis of lidocaine.

Comparison of Injection With EMLA Cream

When comparing mean pain levels for venipuncture following injection of lidocaine with mean pain scores for venipuncture following treatment with EMLA cream $p = .787$. Therefore, there is no significant difference between venipuncture pain whether it is preceded by injection of lidocaine or application of EMLA.

Comparison of Iontophoresis With EMLA Cream

When comparing mean pain scores for venipuncture following iontophoresis of lidocaine and application of EMLA cream $p = .18$. Therefore, there was a significant difference in pain perceived with venipuncture when pretreated with iontophoresis versus EMLA cream. Mean pain scores for venipuncture pretreated with iontophoresis was over twice the mean pain scores for venipuncture following treatment with EMLA. See Table 2 below.

Table 2. Comparison of Pain in Treated Venipunctures

	z	df	p	(sig)	Sig Diff in IV Pain
IV after Injection and Iontophoresis	-2.03	2	.0422	(.02)	No
IV after Injection and EMLA	-.271	2	.7865	(.02)	No
IV after Iontophoresis and EMLA	-2.38	2	.0176	(.02)	Yes

Summary of Results

Local Anesthesia

There was no significant difference in mean pain scores for two of the three anesthetics administered when compared to placebo. Both iontophoresis and its placebo and EMLA cream and its placebo were rated lower in pain experience when compared to injection of lidocaine. There was a significant difference in pain experienced with injection of buffered lidocaine and its placebo whereby buffered lidocaine was rated significantly lower in pain when compared to injection of sterile normal saline. Application of EMLA cream was rated the most comfortable anesthetic ($M=1.5$). Injection of buffered lidocaine was rated the least comfortable anesthetic ($M=12.1$), and the mean pain score for iontophoresis fell in the middle ($M=6.3$).

Venipuncture

There was a significant difference in mean pain scores for venipunctures following treatment with all anesthetics when compared to mean pain scores for venipuncture following treatment with their placebo. There was no significant difference in mean pain scores when comparing venipuncture pain between the three anesthetics with the exception in comparison between venipuncture pain following iontophoresis and venipuncture pain following EMLA cream ($p = .0176$). The mean pain score for venipuncture following iontophoresis was nearly triple that of the mean pain score for venipuncture following treatment with EMLA. The mean pain score for venipuncture following iontophoresis was twice as high as the mean pain score for venipuncture following injection of lidocaine. A summary of all mean pain scores and their significance is found in Table 3 on the following page.

Table 3. Summary of Pain Experiences With Local Anesthesia and Venipuncture

PAIN (in mm)	Treatment 1 Injection Lidocaine (n = 20)			Treatment 2 Iontophoresis Lidocaine (n = 12)			Treatment 3 EMLA Cream (n = 20)		
	M	SD	p	M	SD	p	M	SD	p
Treatment	12.1	11.4	.0020	6.3	12.4	.1070	1.5	4.0	.6800
Placebo	19.9	12.5		0.7	1.8		3.0	11.6	
IV after Anesthetic	7.1	7.2	.0001	15.4	10.1	.0053	6.3	6.7	.0001
IV after Placebo	25.1	13.5		29.5	19.6		27.3	15.2	

In a questionnaire, participants were asked which of the three types of local anesthesia, if any, they prefer for (1) themselves, and for (2) their child, if they or their child were ever to undergo venipuncture? In considering themselves, 58.8% chose EMLA cream and 41.2% chose injection of buffered lidocaine as their preferred method of preparation for venipuncture. No participant preferred "no local anesthetic" prior to venipuncture. When considering their child, 94% chose EMLA cream as their preference. Similarly, no participant chose "no local anesthetic" prior to their child undergoing venipuncture. One participant answered that he or she would not prefer any of the local anesthetics tested in this trial, but would like "some other type" of anesthetic for his child prior to undergoing venipuncture. No participant selected iontophoresis as a preference for either themselves or their children. However, only 12 participants underwent this intervention.

Toleration of Treatments

Twenty individuals underwent two treatments (4 venipunctures and 2 intradermal injections each), and twelve of these participants underwent three treatments (two additional venipunctures following iontophoresis). Four individuals developed mild echymosis (bruising) at the venipuncture site. One individual developed moderately large echymosis bilaterally after the first treatment. Nearly all individuals ($n = 12$) receiving iontophoresis developed mild red blushing under the Meditrode which lasted several minutes. This transient symptom is congruent with the literature and the manufacturer's warning. It is difficult to determine if electrical current or shearing force during removal of the highly-adhesive Meditrode, or both, is responsible for this symptom. Two individuals described a warm, tingling, sensation during iontophoresis at 3mA and required titration to 2mA and 1.5mA before toleration. One individual described an uncomfortable sensation under the return electrode even at 1.5 mA and iontophoresis was discontinued at 7 minutes. This individual sustained the usual red blushing as described in the literature. Neither this participant, or any others, developed cutaneous burns or other complications related to iontophoresis in this study.

One individual developed an erythemic, raised, rash, highly pruritic, approximately 15 minutes following removal of EMLA cream and Tegaderm patch. This completely resolved within one hour with no sequelae. This was the only case in this study highly suspicious for true allergenic reaction to either EMLA cream or the Tegaderm dressing.

CHAPTER FIVE

DISCUSSION

Do patients receiving venipuncture wish for protection from the discomfort of this procedure? The results emphatically demonstrate that all those participating in this study prefer a local anesthetic prior to undergoing venipuncture. Not one participant chose a preference for venipuncture without preparation with a local anesthetic. How do they wish to have their venipuncture site prepared? Roughly half of the participants preferred EMLA cream (59%) and half preferred injection of lidocaine (41%). If their child were to undergo venipuncture, parents overwhelmingly preferred EMLA cream (94%) to injection or iontophoresis of lidocaine.

As was hypothesized, all three local anesthetics provided significantly more comfortable venipunctures, and in some cases, completely painless venipunctures ($n = 10$) when using a local anesthetic beforehand. These findings are supported by the literature (Harrison et al., 1992; Dickey, 1988; Steinbrook et al., 1993).

In this study, both EMLA cream and injection of lidocaine resulted in about the same degree of relief from venipuncture pain with their mean pain scores being low, 6.3mm and 7.1mm respectively. This is consistent with the participants selected anesthetic preferences for EMLA cream and injected lidocaine. Iontophoresis of lidocaine also provided significant relief from venipuncture pain but not to the same degree as its competitors. Mean venipuncture pain after iontophoresis was 15.4mm. This too is consistent with the participants hesitancy to select iontophoresis of lidocaine as an anesthetic preference. Therefore, these findings do not support the third hypothesis of this study which projected iontophoresis to be the preferential local anesthetic.

Just how painful is the administration of each of the local anesthetics? EMLA cream scored lowest in pain ($m = 1.5\text{mm}$), iontophoresis followed ($m = 6.3\text{mm}$), and injection scored highest in pain ($m = 12.1\text{mm}$). Yet, nearly half of the participants (41%) chose injection as their preferred anesthetic. This curious finding may be explained by injected lidocaine's effectiveness in attenuating IV pain. After all, mean venipuncture pain after placebos for injection, iontophoresis, and EMLA were 25.1mm, 29.5mm, and 27.3mm respectively. The tradeoff then, was to experience a mean pain level of 12.1mm with injection of lidocaine to forego as much as a mean pain level of 29.5mm for venipuncture without anesthesia. This amounts to quite a significant savings from pain. In actuality, the very highest pain score for a venipuncture after any placebo was 61.0mm and the very lowest pain score for injection of lidocaine was 0.0mm, therefore the tradeoff in pain-savings for IV puncture can be indeed greater even when administering the "most uncomfortable" of the local anesthetics.

Why venipuncture pain following iontophoresis of lidocaine tended to be two to three times greater than that of its' associates may be explained by the methodology of administration of iontophoresis. In this study, a mean of 8.07 minutes of 2.9 mA was delivered in contention for timeliness and effectiveness of this treatment. Prior studies have reported effective anesthesia with these parameters. Coats and Lupin (1993) found accelerating depths in complete anesthesia of dermis up to 7.5 minutes of application in 7 adults which plateaued at 9 minutes application time. Benefits to anesthesia depths sharply declined with additional application beyond 10 minutes. Maloney et al., (1992) applied a mean mA of 3.4 for a mean duration of 8 minutes to 24 subjects with results demonstrating complete anesthesia in 80% of needle punctures. However, 4% lidocaine with epinephrine was used in this study. Russo et al., (1980) applied 2 to 4 mA over 7 minutes to 12 volunteers. These

individuals then received full-thickness sutures at the treated site. Only one participant reported a dull sensation during suturing.

Perhaps an application time of 10 minutes or more may have provided results reflecting greater anesthesia and lower mean pain scores for venipuncture following iontophoresis as has been described in other literature (Greenbaum & Bernstein, 1994; Zeltzer et al., 1991; Arvidsson et al., 1984; Petelenz et al., 1982).

Another consideration in the popularity of EMLA and injection versus iontophoresis regards the observation that some participants in this study verbalized inconvenience while sitting for iontophoresis of lidocaine for approximately 8 minutes. In comparison, the one-hour absorption requirement for EMLA cream may have gone unnoticed by participants as EMLA cream was applied to the participants by momentarily (about one minute) interrupting their routine at their work location. Although EMLA cream requires a one hour time commitment and iontophoresis requires only about 8 minutes, routines may continue while awaiting EMLA cream to take hold whereas routines come to a halt while recipients are attached to the iontophoresis unit. Popularity for injection of lidocaine, despite another needle prick, may be attributed to the convenience of this effective local anesthetic, typically taking one minute or less.

Relationship of the Findings to the Theoretical Framework

Betty Neuman's Systems Theory (1989) and sensory pain theories served as theoretical frameworks for this study. Neuman believes that each individual or client-system is interconnected with internal and external environmental forces which from time to time become sources of noxious stimuli or stressors. Contending with stressors consumes a portion of the individual's finite energy reserves having the propensity to move the client-system away from homeostasis or

wellness. The goal of nursing is to strategically intervene to eliminate or reduce the negative impact of stressors upon the client-system in order to conserve the individual's energy and maintain a maximum level of wellness.

Is pain from venipuncture a stressor warranting intervention by nursing? All of the participants in this study thought so. All participants chose to have some form of local anesthetic if they were ever to undergo venipuncture again. Similarly, all of the participants chose to have a local anesthetic for their child if he or she were to undergo venipuncture.

The routine procedure of venipuncture may be more important to patients than we have appreciated. In a study by Tuttle (1997) examining what patients believe to be the most important "caring" behaviors by nursing, "knowing how to give IV's" was rated second on a list of 63 nurse caring behaviors (Watson, 1985). These results substantiated a study by Cronin and Harrison (1988) and Larson (1984) which identified nurses' adeptness for caring for IV's to again be one of the most essential nursing responsibilities. It is unknown whether patients have centered on nursing's role in venipuncture because of fear of complications from an improperly placed IV or because of fear of greater pain with an inexperienced or unskilled cannulator. It is possible both concerns have lead to patients rating IV's as the second most important nurse caring behavior in Tuttle's study. These findings are congruent with Hamilton's (1994) citation for the new medical diagnosis, "needle phobia" affecting an estimated 10% of the population. Venipuncture appears to be a greater concern and potential stressor to patients than we had judged.

Would elimination of venipuncture pain result in greater energy and coping by patients for other stressors they may face? Although direct measurement for this may be improbable, we know pain to be taxing. Diagnostic and procedural pain in a hospital setting where individuals are already faced with other adversities, may tax

individuals at an even higher rate. Therefore, eliminating procedural pain might reap greater energy savings in this setting. It is noteworthy that all individuals in this study were free from acute or chronic illness, yet all still preferred to have their venipuncture pain attenuated with a local anesthetic.

The implications for nursing seem clear. The findings of this study support well-documented, nearly-unanimous clinical trials establishing the safety and efficacy of lidocaine as a local anesthetic for venipuncture. What may be lacking however, are clinician's willingness to acknowledge venipuncture pain as a stressor for patients and willingness to make the changes in clinical practice necessary to alleviate this stressor.

Strengths, Limitations, and Recommendations

This study may stand alone in that to this researcher's knowledge, there exist no other trials measuring toleration of three different local delivery methods for lidocaine as well as placebos in one sample. The study is further unique in that these same individuals went on to undergo venipuncture following each different anesthetic treatment as well as placebos for each. The group was then given an opportunity to express which treatment, if any, was preferred for themselves and their children. A Bonferonni correction was applied in this analysis providing more rigorous estimation of the true probability of erroneously concluding a comparison to be significant. Therefore, there is greater confidence in the significant differences found in this study.

This study is very limited by the small volunteer sample utilized. However, the number of participants in this study is consistent with the number of subjects found in similar trials where volunteers are asked to subject themselves to painful experimental interventions. Nonetheless, the results of this study cannot assuredly

be generalized to the public. The participants of this study were from medical and paramedical professions which would be expected to bias the results of this study as well.

It is recommended that further clinical trials compare the safety and effectiveness, as well as the public's wishes, regarding local anesthesia before venipuncture. Larger, randomized samples will lend credence to existing research. Examination of the three modalities should be expanded to include anesthesia before other hospital or outpatient procedures which are known to be painful, but have historically gone untreated. Current research has so emphatically identified venipuncture pain to be relieved by anesthetic treatment, when compared to placebo, future studies may consider elimination of placebo, in order to zero in on study for more efficient uses of existing and new modalities of local anesthesia.

The safety and effectiveness of EMLA cream for venipuncture in children has been established in depth in the literature. Further studies are called for to expand beyond the superior qualities of EMLA cream to examine the disadvantages of EMLA cream, specifically the timeliness required (one hour) for onset of dermal anesthesia. Sonophoresis is being studied as a potential mechanism of ultrasound-enhanced transdermal drug delivery and may prove to accelerate the effects of topical anesthetics such as EMLA cream (Bommannan, et al., 1992).

Conclusion

The results of this study show that the three common reasons given by clinicians for not using a local anesthetic prior to venipuncture are invalid. Venipuncture has been shown to be a stressor for patients for which they desire relief. Administration of the local anesthetic lidocaine, whether given by injection,

iontophoresis, or topically, is far less painful than venipuncture itself. All three methods of delivery of lidocaine have been documented in the literature to be safe in adults to which this study can add.

EMLA cream demonstrated superiority over injection and iontophoresis of lidocaine. EMLA was the most comfortable anesthetic treatment, it provided for the most comfortable venipuncture, and it was overwhelmingly chosen preferential by the participants when considering venipuncture in children and somewhat preferential over injection of lidocaine when considering themselves.

The findings of this study as well as the review of the literature presented, support the use of EMLA cream and injection of lidocaine as local anesthetics in eliminating the pain of venipuncture. Further investigation into practicality and effectiveness of iontophoresis as an anesthetic for venipuncture will likely reinforce iontophoresis to be an effective modality on the menu of pain-relieving measures.

This researcher suspects that the added time and cost in offering patients a local anesthetic before venipuncture, will continue to allow rationalization by clinicians and institutions against the use of a local anesthetic. Without organized advocacy by a profession, the unsuspecting public will be powerless to insist on this hidden and humane clinical practice.

Appendix A
Visual Analog Scales

Please place a single mark upon the line which represents the amount of pain you experienced with each procedure. The left margin of the line represents no pain at all and the right margin of the line represents worst pain.

Meeting #

NO PAIN MILD PAIN MODERATE PAIN WORST PAIN

NO PAIN MILD PAIN MODERATE PAIN WORST PAIN

NO PAIN MILD PAIN MODERATE PAIN WORST PAIN

NO PAIN MILD PAIN MODERATE PAIN WORST PAIN

Appendix B

Questionnaire

Please select one answer for each question by placing a check mark by your answer.

A. Which of the three delivery methods for the local anesthetic lidocaine, did you prefer?

- 1.____ Injection of lidocaine (meeting #1)
- 2.____ Iontophoresis of lidocaine (meeting #2)
- 3.____ Topical application of EMLA cream (meeting #3)
- 4.____ I did not care for any of the above local anesthetics, but I would like to have my arm numbed before venipuncture
- 5.____ I do not wish to receive a local anesthetic before undergoing venipuncture

If your child were to undergo venipuncture, which method of local anesthesia would you prefer for him or her to receive?

- 1.____ Injection of lidocaine
- 2.____ Iontophoresis of lidocaine
- 3.____ Topical application of EMLA cream
- 4.____ I do not wish my child to receive any of the above local anesthetics, but I would prefer my child's arm to be numbed before undergoing venipuncture.
- 5.____ I do not wish for my child to receive a local anesthetic before undergoing venipuncture

Please answer:

Male____ Female____

Age_____

Appendix C

Consent Form

**THIS IS A PROSPECTIVE STUDY TO DETERMINE THE EFFECTIVENESS, IF ANY, OF
INTRADERMAL LIDOCAINE COMPARED WITH LIDOCAINE BY IONOPHORESIS,
COMPARED WITH TOPICAL LIDOCAINE/PRILOCAINE CREAM AS LOCAL
ANESTHETICS IN VENIPUNCTURE**

PRINCIPAL INVESTIGATOR: Carol Straight, R.N.

PURPOSE: I AM BEING ASKED TO PARTICIPATE IN A RESEARCH STUDY INVOLVING:
1) THE ADMINISTRATION OF THE DRUG LIDOCAINE (1% CONCENTRATION)
UNDER MY SKIN BY INJECTION AND BY PROPULSION OF LIDOCAINE (2 %
CONCENTRATION) UNDER MY SKIN, AND BY DIFFUSION OF LIDOCAINE /
PRILOCAINE CREAM TOPICALLY (CONCENTRATION OF 5%) UNDER MY SKIN,
PRIOR TO VENIPUNCTURE WITH A 20 GAGE IV CATHETER FOLLOWING EACH
TREATMENT FOR A TOTAL OF SIX IV STARTS (TWO IV STARTS ON THREE
SEPARATE OCCASIONS
2) COMPLETE A PAIN ASSESSMENT SCALE AND THREE QUESTIONS REQUIRING
ONE TO FIVE MINUTES

It has been explained to me that Lidocaine and Prilocaine are drugs widely used as a local anesthetic. Lidocaine and Prilocaine, administered in this study, are standard concentrations and amounts, safely providing local anesthesia of a surface area approximately two cm in diameter for approximately 30 to 60 minutes. **Allergic reactions to Lidocaine and Prilocaine have been known to occur on rare occasion. Sensitivity or allergic reactions can range from brief redness and itching of the skin to difficulty breathing. I understand that if I have a known allergy or sensitivity to Lidocaine or Prilocaine, I cannot participate in this study. I also understand that if I am currently taking a Sulfa medication, I cannot participate in this study. In addition, I understand that if I have a major or chronic illness, I am pregnant, I have a pacemaker or automatic implantable defibrillator, or I have a condition called Glucose-6-Phosphate Dehydrogenase Deficiency, I cannot participate in this study.** The purpose of this research study is to determine whether the pain-reducing effects of lidocaine solution and lidocaine/prilocaine cream can be applied effectively in venipuncture. Approximately twenty-five volunteers will be sought for this study.

PROCEDURE:

If I agree to participate in this research study, the following will be expected of me.

- 1) **Meeting #1:** Receive an intradermal injection of 0.5cc of 1% lidocaine into the right or left forearm followed by placement of a 20 g Insite IV catheter.
Receive an intradermal injection of 1 cc of sterile normal saline into the right or left forearm followed by placement of a Insite 20 g IV catheter.

Approximately 1 week later:

Meeting # 2: Receive a needleless injection of 2% lidocaine using a small and usually undetectable electrical current (1.5-3mAmps) for approximately eight minutes into the right or left forearm followed by placement of a 20 g Insite IV catheter. Receive a needleless injection of normal saline using the same technique followed by placement of a 20 g Insite IV catheter.

Approximately 1 week later:

Meeting #3: Receive topically 2.5 g of EMLA cream (lidocaine 2.5% and prilocaine 2.5%) upon about a 2 inch by 2 inch surface area on the right or left forearm followed by placement of a clear occlusive dressing placed over the cream. The dressing and cream will be completely removed 1 hour later and a 20 g Insite IV catheter inserted. Receive topically an unmedicated cream upon about a 2 inch by 2 inch surface area on the right or left forearm followed by placement of a clear occlusive dressing placed over the cream. The dressing and cream will be completely removed 1 hour later and a 20 g Insite IV catheter will be inserted.

- 2) Complete a visual pain scale after each venipuncture requiring approximately one to two minutes and complete three questions after the three treatments
- 3) Removal of each IV catheter and placement of a bandaid to be removed in 2 hours
- 4) Observe the venipuncture site for 24 hours from procedure and contact the researcher if the following symptoms should occur: swelling or redness at the site, itching or pain at the site, a rash at the site or elsewhere, or any new or unusual symptoms.
- 5) I understand that I will be contacted by the researcher approximately 24 hours after each meeting in evaluation for side effects.

RISKS/BENEFITS:

Very rarely, individuals may be allergic or sensitive to Lidocaine or Prilocaine. Symptoms of allergy can range from mild redness or itching at the site to difficulty breathing.

The results of this study may help clinicians to identify Lidocaine and Lidocaine /Prilocaine cream as a safe and effective local anesthetic for the procedure of venipuncture.

My participation in this study is voluntary. No payment for participation will be given. I understand that in the event of injury or illness resulting from the study, no compensation, free medical care or reimbursement is offered by Grand Valley State University or by the researcher. I understand that I am free to withdraw my

consent to participate in this research study at any time and for any reason.

CONFIDENTIALITY:

I understand that my participation in this research study is strictly confidential. The records of the study will be kept by the researcher and will be shared with only key nursing faculty of Grand Valley State University. The results of the study may be shared with groups and organizations and may even be published. However, no information by which I may be identified will be released or published. In the event I require medical care as a result of this research study, details of the research study may be released to the individual(s) involved in my care.

I have read or have had read to me all the above information about this research study, including the research procedure, possible risks and side effects, and the likelihood of benefits from the study.

The content and meaning of this information has been explained and is understood by me. All of my questions have been answered. I hereby consent and voluntarily offer to follow the study requirements and take part in the study. I understand that I will receive a signed copy of this consent form.

If I have any questions concerning my participation in this study now, or in the future, I may contact Carol Straight, R.N. at (616) 938-1165 or Professor Paul Huizenga at (616) 895-2472.

Research Participant's Name _____

Research Participant's Home Phone # _____

Research Participant's Signature _____

Date Signed _____

Witness _____

Date Signed _____

I am interested in receiving a summary of the study results. Yes _____ No _____

Life-Tech, Inc.

10920 Kinghurst • Houston, TX 77099

713-495-9411 • Fax: 713-495-7960 • 1-800-231-9841



NeedleBuster® Setup Chart Meditrode (6570) and Gel-Trode (6585)

Age	0-2 Yrs.		2-6 Yrs.		6+ Yrs. / Patient Comfort Level
Current	.5	1	2	3	4
Time	20	15	10	7.5	5
Meditrode Fluid Capacity	Bandaid 6570S 1.5 CC	Small Square 6570M 2 CC		Large Square 6570L 7 CC	Round Return 6570R 6 CC

Skin Preparation

1. Inspect site for skin imperfections.

Caution: Do not place electrode over skin imperfections such as moles, scars, warts, or damaged skin. If can not be avoided, insulate damaged area by applying Vaseline with a Q-tip over imperfection only. Clip excessive hair if necessary. Do not shave treatment area within 24 hours before treatment.

2. Wipe with alcohol swab and let dry

Caution: Do not abrade



6570(x)



6585(xx)

Meditrode Application

1. Remove backing from 6570(x)Meditrode®
2. Apply to clean & dry treatment area. slightly stretching while applying to remove all wrinkles
3. Connect the red NeedleBuster lead wire to the active drug delivery Meditrode® (6570 series)
4. Remove backing from the 6585(xx) self adhering dispersive Gel-Trode
5. Apply to clean & dry treatment area starting from the center and pressing towards the end to smooth all wrinkles
6. Connect the black NeedleBuster® lead wire to the self adhering dispersive Gel-Trode
7. Saturate the 6570(x)active drug delivery Meditrode with drug solution by placing the syringe tip into the fill ports and injecting fluid until electrode saturation is achieved.

Meditrode Fluid Capacity	Bandaid 6570S 1.5 CC	Small Square 6570M 2 CC	Large Square 6570L 7 CC	Round Return 6570R 6 CC
--------------------------------	----------------------------	-------------------------------	-------------------------------	-------------------------------

NeedleBuster ® Connection

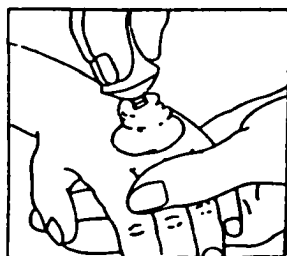
1. Connect leads to NeedleBuster® by connecting the read lead to the red connector labeled "Drug (+)" and the black lead to the black connector labeled "RTRN (-)"
2. Turn on NeedleBuster® by pressing the key pad labeled "On/Off" and observing that the "PWR" light is on and the "OPN" light is off. If "OPN" occurs, consult NeedleBuster operating manual.
3. Set Current as shown above by rotating Current knob clockwise to increase delivery time and counter clockwise to decrease delivery time
4. Set Time as shown above by rotating Time knob clockwise to increase delivery time and counter clockwise to decrease delivery time.

Appendix E

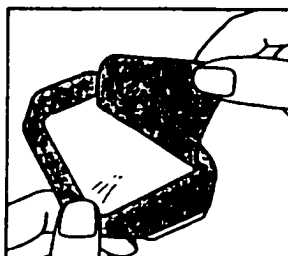
Astra Pharmaceutical Insert Instruction for the Use of EMLA Cream

EMLA[®]

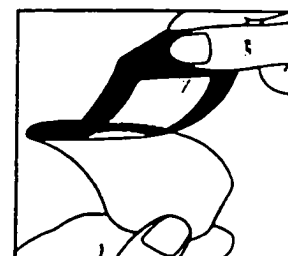
CREAM (lidocaine 2.5%
and prilocaine 2.5%)



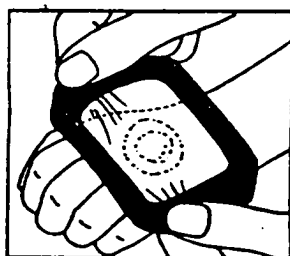
1. Apply 2.5 g of cream (1/2 the 5 g tube) per 20 to 25 cm² (approx. 2 in. by 2 in.) of skin in a thick layer at the site of the procedure.



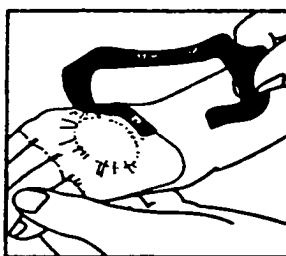
2. Take an occlusive dressing (provided with the 5 g tubes only) and remove the center cut-out piece.



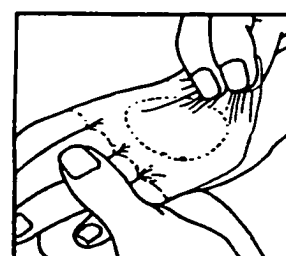
3. Peel the paper liner from the paper framed dressing. (Instructions continued on reverse side.)



4. Cover the EMLA[®] Cream so that you get a thick layer underneath. Do not spread out the cream. Smooth down the dressing edges carefully and ensure it is secure to avoid leakage. (This is especially important when the patient is a child.)



5. Remove the paper frame. The time of application can easily be marked directly on the occlusive dressing. EMLA[®] must be applied at least 1 hour before the start of a routine procedure and for 2 hours before the start of a painful procedure.



6. Remove the occlusive dressing, wipe off the EMLA[®] Cream, clean the entire area with an antiseptic solution and prepare the patient for the procedure. The duration of effective skin anesthesia will be at least 1 hour after removal of the occlusive dressing.



APPLETON & LANGE

Simon & Schuster
International and Business & Professional Group
107 Elm Street, P.O. Box 120041
Stamford, CT 06912-0041
203-406-4500 • Fax: 203-406-4601

December 15, 1997

Carol Straight, RN
2063 Holiday Place
Traverse City, MI 49686

Dear Ms. Straight:

Thank you for your inquiry regarding obtaining permission to reproduce:

Author(s): Betty Neuman, PhD, FAAN

Title: The Neuman Systems Model: Third Edition (1995)

Figure(s)/Table(s): Figure 1-1, p.17

in your Grand Valley State University masters thesis, "Comparison of the Effectiveness of Intradermal Injection of Lidocaine, Isotophoretic Delivery of Lidocaine, and Topical Emla Cream as Local Anesthetics for Venipuncture," to be completed in November 1997.

Permission is granted subject to your research confirming that the material in question is original to our text. Permission is granted on a non-exclusive, one-time only or life of edition basis, with distribution rights throughout the world in print only. Permission must be requested separately for electronic rights and derivative works. Permission is granted subject to:

1. Use of a credit line which must include the name of the author, title of the book, edition, copyright holder (Appleton & Lange), and year of publication. The credit line must appear on the same page as our text or illustration.
2. Permission of the author.

If you have any questions, please feel free to contact me.

Sincerely,

A large black rectangular box redacting the signature of the Permissions Editor.

Permissions Editor
Phone (203) 406-4627

REFERENCES

- Adriani, J., Coffman, V., Naraghi, M. (1986). The allergenicity of lidocaine and other amide type local anesthetics. Anesthesiology Review, 13, 30-36.
- Armel, H. E., Horowitz, M. (1993). Alkalinization of local anesthesia with sodium bicarbonate-preferred method of local anesthesia. Urology, 43, 101-102.
- Arvidsson, S. B., Erroth, R. H., Hansby, A. M., Lindholm, A. H., Whinam-Olsson, G. (1984). Painless venipuncture. A clinical trial of iontophoresis of lidocaine for venipuncture in blood donors. Acta Anesthesiology of Scandinavia, 28, 209-210.
- Astra Pharmaceuticals. (1996). Manufacturer's Insert on EMLA Cream.
- Bjerring, P., Anderson, P. H., Arendt-Nielson, L. (1989). Vascular response of human skin after analgesia with EMLA cream. British Journal of Anesthesia, 63, 655-660.
- Bommannan, D., Gopinathan, K., Menon, H., Elias, P., Guy, R. (1992). Sonophoresis. Examination of the Mechanism(s) of Ultrasound-enhanced transdermal drug delivery. Pharmaceutical Research, 9, 1043-1047.
- Brownlee, S. Schrof, J. M. (1997, March 17). The quality of mercy. U.S. News & World Report.
- Buckley, M. M., Benfield, P. (1993). Eutectic lidocaine/prilocaine cream. A review of the topical anesthetic/analgesic efficacy of a eutectic mixture of local anesthetics (EMLA). Drugs, 46, 126-151.
- Cartwright, P., McLaughlin, F., Martinez, A., Caul, D., Hogan, I., Reed, G., Swafford, m. (1993). Teenagers' perceptions of barriers to prenatal care. Southern Medical Journal, 86, 737-741.
- Chang, P., Goresky, G., O'Connor, G., Pyesmany, D., Rogers, P., Steward,, D., Stewart, J. (1993). A multicenter randomized study of single-unit dose package of EMLA patch vs EMLA 5% cream for venipuncture in children. Canadian Journal of Anesthesia, 59-63.
- Chein, Y. W., Banga, A. K. (1989). Iontophoretic (Transdermal) delivery of drugs: overview of historical development. Journal of Pharmaceutical Sciences, 78, 353-354.

Chein, Y. W., Siddiqui, O., Shi, W. M., Lelawongs, P., Liu, J. C. (1989). Direct current iontophoretic transdermal delivery of peptide and protein drugs. Journal of Pharmaceutical Sciences, 78, 376-383.

Chrighnton, Alexander, J. (1992). Reducing pain associated with injection of lidocaine. British Medical Journal, 305, 954-955.

Christoph, R. A., Buchanan, L., Begalla, K., Schwartz, S. (1988). Annals of Emergency Medicine, 17, 117-120.

Clark, S., Radford, M. (1996). Topical anesthesia for venipuncture. Journal of the British Paediatric Association, 61, 1132-1134.

Coats, A. C., Lupin, L. C. (1995). Iontophoretic delivery of lidocaine for local surface anesthesia-effect of drug concentration and test and subject parameters. Life-Tech, Inc. Houston, Texas.

Cooper, C. M., Gerrisg, S. P., Hardwick, M., Kay, R. (1987). EMLA cream reduces the pain of venipuncture in children. European Journal of Anesthesiology, 4, 441-448.

Costello, C. T. (1992). The optimization of drug delivery with iontophoresis. Unpublished doctoral dissertation, Texas Woman Hospital, Houston.

Cragg, A. H., Berbaum, K., Smith, T. P. (1987). A prospective trial of warm and cold lidocaine for intradermal injection. AJR, 150, 1183-1184.

Cronin, S. & Harrison, B. (1988). Importance of nurse caring behaviors as perceived by patients after myocardial infarction. Heart & Lung, 22, 374-380.

Dalton, A. M., Sharma, A., Redwood, M., Wadsworth, J., Touquet, R. (1989). Does the warming of local anesthetic reduce the pain of its injection? Archives of Emergency Medicine, 6, 247-250.

Davidson, J. A., Boom, S. J. (1992). Warming lidocaine to reduce pain associated with injection. British Medical Journal, 305, 617-618.

Dick, M. J., Maree, S. M., Gray, J. (1992). How to boost the odds of a painless IV start. American Journal of Nursing, 92, 49-50

Dickey, J. (1988). Effectiveness of intradermally injected lidocaine hydrochloride as a local anesthetic for intravenous catheter insertion. Journal of Emergency Nursing, 14, 160-163.

Ellinwood, E. H., Hamilton, J. G. Case report of a needle phobia. Journal of Family Practice, 32, 420-423.

Engel, G. L. (1978). Psychologic stress, vasodepressor (vasovagal) syncope and sudden death. Annals of Internal Medicine, 89, 403-412.

Evers, H., Von Dardel, O., Juhlin, L., Ohlsen, L., Vinnars, E. (1985). Dermal effects of compositions based on the eutectic mixture of lidocaine and prilocaine (EMLA). British Journal of Anesthesiology, 57, 997-1005.

Farley, J. S., Hustead, R. F., Becker, K. E. (1994). Diluting lidocaine and mepivacaine in balanced salt solution reduces the pain of intradermal injection. Regional Anesthesia, 19(1), 48-51.

Fay, M. F. (1989). Indications and applications for iontophoresis. Today's OR Nurse, 11, 10-31.

Galena, H. J., (1992). Complications occurring from diagnostic venipuncture. Journal of Family Practice, 34, 582-584.

Gangarosa, L. P. (1993). Iontophoresis in pain control. Pain Digest, 3, 162-174.

Gift, A. G. (1989). Visual analogue scales: measurement of subjective phenomena. Nursing Research, 38, 286-288.

Glantz, S. A. (1992). Primer of Biostatistics. (3rd ed). McGraw Hill, New York.

Goldstein, D., Sparnakal, M., Pitterman, A., Toltzis, A., Gratz, E., Epstein, S., Keiserr, H. (1982). Circulatory control mechanisms in vasodepressor syncope. American Heart Journal, 104, 1071-1075.

Greenbaum, S. S., Bernstein, E. F. (1994). Journal of Dermatological Surgical Oncology, 20, 579-583.

Gunawardene, R., Davenport, H., (1990). Local application of EMLA and glyceryl trinitrate ointment before venipuncture. Anesthesia, 45, 52-54.

Hamilton, J. G. (1995). Needle phobia: a neglected diagnosis. Journal of Family Practice, 41, 169-174.

Harrison, N., Langham, B., Bogod, D. D. (1992). Appropriate use of local anesthetic for venous cannulation. Anaesthesia, 47, 210-212.

Joyce, Thomas. (1993). Topical anesthesia and pain management before venipuncture. Journal of Pediatrics, 122, 24-28.

Joyce, T. H., Skjonssby, B. S., Taylor, B. D., Morrow, D. H., Hess, K. R. (1992). Dermal anesthesia using a eutectic mixture of lidocaine and prilocaine (EMLA) for venipuncture in children. Pain Digest, 2, 137-141.

Juarez, Gloria. (1997). Culture and pain. Pain Management, 4, 86-90.

Juhlin, L., Hagglund, G., Evers, H. (1989). Absorption of lidocaine and prilocaine after application of the eutectic mixture of local anesthetics (EMLA) on normal and diseased skin. Acta DermatoVenereologica, 69, 18-22.

Juhlin, L., Evers, H. (1990). EMLA: a new topical anesthetic. Advances in Dermatology, 5, 75-92.

Kurian, L., Kollberg, H., Uppfeldt, A. (1985). Venipuncture pain can be reduced. Journal of Topical Medicine and Hygiene, 88, 397-399.

Langham, B. T., Harrison, D. A. (1992). Local anesthetic: does it really reduce the pain of insertion of all sizes of venous cannula? Anaesthesia, 47, 890-891.

Larson, P. (1995). Oncology nurses as caregivers: Important nurse caring behaviors perceived by patients with cancer. Oncology Nursing Forum, 22, 481-487.

Latham, J. (1994). Assessment and measurement of pain. European Journal of Cancer Care, 3, 75-78.

Lee, J. J., Rubin, A. P. (1993). EMLA cream and its current uses. British Journal of Hospital Medicine, 50, 463-466.

Leeming, M. N. (1970). Low voltage direct-current burns. JAMA, 214, 1681-1684

Ludwig-Beymer, P., Huether, S., Schossler. (1994). Pain, temperature regulation, sleep, and sensory function. In K. L. McCance & S. E. Huether (2nd ed.) Pathophysiology: The basis for disease in adults and children (pp. 437-478). St. Louis: Mosby.

Maddi, R., Horrow, J., Mark, J., Concepcion, M., Murray, E. (1990). Evaluation of a new cutaneous topical anesthesia preparation. Regional Anesthesia, 15, 109-112.

Mader, T. J., Playe, S. J., Garb, J. L. (1993). Reducing the pain of local anesthetic infiltration: Warming and buffering have a synergistic effect. Annals of Emergency Medicine, 23, 550-554.

Maloney, M. J., Bezzant, J. L., Stephen, R. L., Petelenz, T. J. (1992). Iontophoretic administration of lidocaine anesthesia in office practice. Journal of Dermatological Surgical Oncology, 18, 937-940.

Marks, I. (1988). Blood-injury phobia: a review. American Journal of Psychiatry, 145, 1207-1213.

Martin, S., Jones, J. S., Wynn, B. N. (1996). Does warming local anesthetic reduce the pain of subcutaneous injection? American Journal of Emergency Medicine, 14, 10-12.

Moller, C. A., (1985). Lidocaine-prilocaine cream reduces venipuncture pain. Journal of Medical Sciences, 90, 293-298.

Morris, R. W., McKay, W., Mushlin, P. (1987). Comparison of pain associated with intradermal and subcutaneous infiltration with various local anesthetic solutions. Anesthesia Analogs, 66, 1180-1182.

Morris, R. W., Whish, K. M. (1984). A controlled trial of pain in skin infiltration with local anesthetics. Anesthesia Intensive Care, 12, 113-114.

Neuman, B. M. (1989). Health as a continuum based on the Neuman Systems Model. Nursing Science Quarterly, 129-135.

Neuman, B. M. (1989). The Neuman Systems Model. (2'nd ed.) Appleton & Lange, Norwalk, CT.

Neuman, B. M. (1995). The Neuman Systems Model. (3'rd ed.) Appleton & Lange, Norwalk, CCT.

Nott, M., Peacock, J. (1990). Relief of injection pain in adults. EMLA cream for 5 minutes before venipuncture. Anesthesia, 45, 772-774.

Okabe, K., Yamaguchi, H., Kawai, Y. (1987). New iontophoretic transdermal administration of the beta blocker metoprolol. Journal of Controlled Release, 4, 79-85.

Ost, L. G. (1991). Acquisition of blood and injection phobia and anxiety response patterns in clinical patients. Behavioral Res Therapy, 29, 323-332.

Petelenz, T., Axenti, I., Petelenz, J., Iwinski, J., Dubel, S. (1982). Mini set for iontophoresis for topical analgesia before injection. Paper presented at the meeting of the 3'rd Chair of Cardiology and the Clinic of Cardiology of the Silesian Medical Academy Katowice; of the Research and Development Center of Electronic Medical Equipment, Zabrze, Group Poland.

Physicians' Desk Reference. (1995). 49th ed. Medical Economics Data, Montale.

Robieux, I., Eliopoulos, C., Hwang, P., Greenberg, M., Blanchette, V. (1992). Pain perception and effectiveness of the eutectic mixture of local anesthetics in children undergoing venipuncture. Pediatric Research, 32, 520-523.

Robieux, I., Kumar, R., Radhakrishnan, S., Koren, G. (1991). Assessing pain and analgesia with a lidocaine-prilocaine emulsion in infants and toddlers during venipuncture. Journal of Pediatrics, 118, 971-973.

Rose, R. M., Hurst, M. W. (1975). Plasma cortisol and human growth hormone responses in intravenous catheterization. Journal of Human Stress, 1, 22-36.

Rubin, J. J., Lee, A. P. (1993). EMLA cream and its current uses. British Journal of Hospital Medicine, 50, 463-467.

Russo, J., Lipman, A. G., Comstock, T. J., Page, B. C., Stephen, R. L. (1980). Lidocaine anesthesia: Comparison of iontophoresis, injection, and swabbing. American Journal of Hospital Pharmacy, 37, 843-847.

Scott, J. & Huskisson, E. (1979). Accuracy of subjective measurements made with or without previous scores: An important source of error in serial measurement of subjective states, Annals of Rheumatic Diseases, 38, 558-559.

Singh, P., Roberts, M. S. (1993). Iontophoretic transdermal delivery of salicylic acid and lidocaine to local subcutaneous tissue. Journal of Pharmaceutical Sciences, 82, 127-131.

Smith, M. C. (1989). Neuman's Model in Practice. Nursing Science Quarterly, 116-117.

Steinbrook, R. A., Hughes, N., Fanciullo, G., Manzi, D., Ferrante, F. M. (1993). Effects of alkalization of lidocaine on the pain of skin infiltration and intravenous catheterization, Journal of Clinical Anesthesia, 5, 456-458.

Taggart, P., Hedworth-Whitty, R., Carruthers, M., Gordon, P. D. (1976). Observations of electrocardiogram and plasma catecholamines during dental procedures: the forgotten vagus. British Medical Journal, 2, 787-789.

Tuttle, S. (1997). Patient perceptions of nurse behaviors as indicators of caring. Unpublished master's thesis, Grand Valley State University, Grand Rapids, Michigan.

Villada, G., Zetlaoui, J., Revuz, J. (1990). Local blanching after epicutaneous application of EMLA cream. Dermatologica, 181, 38-40.

Watson, J. (11979). Nursing: The philosophy and science of caring. Boston: Little, Brown.

Wewers, M. E., Lowe, N. K. (1990). A crtitical view of visual analogue scales in the measurement of clinical phenomena. Research in Nursing & Health, 13, 227-236.

Wolf, S., Shier, J., Lampl, K., Schwartz, R. (1994). EMLA cream for painless skin testing: a preliminary report. Annals of Allergy, 73, 40-42.

Zeltzer, L., Regalado, M., Nichter, L. S., Barton, D., Jennings, S., Pitt, L. (1991). Iontophoresis versus subcutaneous injection: A comparison of two methods of local anesthesia delivery in children. Pain, 44, 73-78.