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A COMPARISON OF GENDER DIFFERENCES IN THE EFFECTS OF PREEMPTIVE KETAMINE ON PERCIEVED PAIN IN MALES AND FEMALES UNDERGOING SELECTED EAR, NOSE, AND THROAT SURGICAL PROCEDURES

By

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A Cluster Research Study

submitted in partial fulfillment

of the requirements for the degree of

Master of Science in Nursing

The University of Texas Health Science Center at Houston

School of Nursing

December, 2003

Abstract

Postoperative pain leads to increased morbidity, length of stay, and health care costs. Several studies have shown that preemptively administered N-methyl-D-aspartate (NMDA) antagonists, such as ketamine, are effective in decreasing perception of postoperative pain. To date, there have not been any human studies to investigate a gender difference in NMDA receptor antagonism. The purpose of this study was to compare the gender differences in the effects of preemptive ketamine on perceived pain in males and females undergoing selected ENT surgical procedures. This prospective, double-blinded study compared perceived pain in male and female subjects drawn from a convenience sample of patients at a major military medical center. The surgeries these patients were presenting for were tonsillectomy, adenoidectomy, tonsillectomy and adenoidectomy (T&A) and uvulopalatopharyngoplasty (UPPP). 41 subjects were randomly assigned to either a treatment group receiving .1 mg/kg ketamine or a control group receiving a placebo of .9% saline. The study drug was administered between induction and incision. Pain perception following surgery was measured using a Numeric Rating Scale (NRS) on arrival to the post anesthesia care unit (PACU), and at four subsequent data points (1, 4, 12, 24 hours after PACU arrival time). ANOVA and Friedman tests were used to analyze the NRS scores. The ANOVA test did not show a significant difference ($p = .768$) in postoperative pain perception between males and females who received preemptive ketamine. The Friedman test did not show a significant difference ($p = .27$) in the level of postoperative pain perception within the groups over the five data collection points.

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A COMPARISON OF GENDER DIFFERENCES IN THE EFFECTS OF PREEMPTIVE KETAMINE ON PERCIEVED PAIN IN MALES AND FEMALES UNDERGOING SELECTED EAR, NOSE, AND THROAT SURGICAL PROCEDURES

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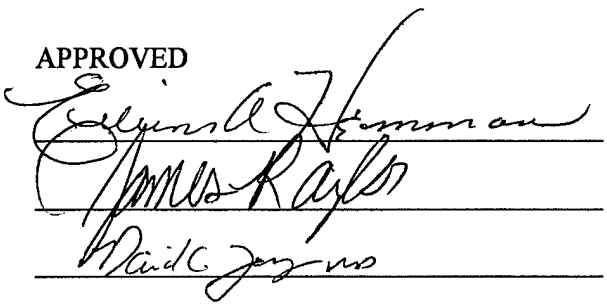

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NOTICE OF APPROVAL TO BEGIN RESEARCH November 15, 2002

HSC-SN-02-030 "A Comparison of Gender Differences in Perceived Pain following Preemptive Ketamine in Patients Undergoing Selected Ear, Nose and Throat Surgery"
P.I.: Dennis Turner, MSN Student; Robert Ladd, MSN Student; Carrie Pike, MSN Students; Brian Baumgartner, MSN Student

PROVISIONS: Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consent, etc.

APPROVED: At a Convened Meeting

APPROVAL DATE: November 15, 2002 EXPIRATION DATE: October 31, 2003

CHAIRPERSON: Anne Dougherty, MD

Subject to any provisions noted above, you may now begin this research.

CHANGES: The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.

INFORMED CONSENT: Informed consent must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. **Please note that only copies of the stamped approved informed consent form can be used when obtaining consent.**

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

RECORDS: The PI will maintain adequate records, including signed consent documents if required, in a manner that ensures subject confidentiality.

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REPLY TO ATTENTION OF:

10 October 2002

Department of Clinical Investigation

SUBJECT: Research protocol: A Comparison Of Gender Differences In Perceived Pain Following Preemptive Ketamine In Patients Undergoing Selected Ear, Nose, and Throat Surgery

CPT Dennis R. Turner, AN
Anesthesia Student
USA Grad Program in Anesthesia Nursing
Madigan Army Medical Center
Tacoma, WA 98431

1. The subject protocol and the accompanying consent form were reviewed and approved by the Institutional Review Board at Madigan Army Medical Center, 24 September 2002.

2. The protocol and consent form (dated 25 Sep 02), revised in accordance with recommendations from the IRB, have been reviewed and approved by the Chairman, IRB, in accordance with IRB regulations.

3. The protocol has been assigned MAMC #202119 and may now be implemented. A copy of the minutes of the IRB meeting, a copy of the approved consent form and a copy of the protocol are attached.

4 The protocol is approved for a period of one year and must be reapproved for continuation by the Institutional Review Board no later than 23 September 2003. Failure to comply with the continuing review process within the protocol's initial approval period (10 Oct 02 through 23 Sep 03) will result in suspension of the protocol.

5 If changes are made to the protocol, a request for a revision must be forwarded to the Chairman, IRB, and approved by the IRB, prior to implementation of changes. If any change affects the consent form, a revised copy of the consent form should also be submitted to the Chairman, IRB, and approved by the IRB, prior to its implementation.

6. When the protocol is completed or terminated, you must report this to the Department of Clinical Investigation.

7. In accordance with AR 40-38, the principal investigator must report any serious or unexpected adverse reactions to drugs or procedures to the IRB through the Chief, Department of Clinical Investigation. AR 40-7 and 21 CFR 312.32 define a serious adverse reaction as one that results in:

(1) death
(2) a life-threatening situation
(3) persistent or significant disability/incapacity
(4) inpatient or prolonged hospitalization
(5) congenital anomaly/birth defect in an offspring
(6) an important medical event that, based upon appropriate medical judgment may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

ROBERT E. RICKS, M.D.
COL, MC
Chairman, IRB

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CHAPTER I

Introduction

Seventy-seven percent of male and female patients complain of postoperative pain following surgery, and many of those who complain of postoperative pain rate it as moderate to severe (Warfield & Kahn, 1995). If untreated or inadequately treated; postoperative pain may result in a physiologic stress response that is physically demanding and even life threatening for certain patients. The stress response that can be brought about by intense pain is associated with increased sympathetic tone secondary to catecholamine release which in turn leads to increased myocardial work, heart rate, blood pressure, and oxygen consumption, all of which increase the risk of ischemic events (Rawal, 1998; Rosenberg & Kehlet, 1999). Inadequate pain management may also compromise respiratory status resulting in difficulty with the ability to breathe deeply and cough effectively as well as decreased vital and functional residual capacity, atelectasis and pneumonia (Cushieri, Morran, & McArdle, 1985). Pulmonary status may also be compromised by opioid related respiratory depression when postoperative pain warrants increased opioid consumption. The physiologic consequences of poorly managed postoperative pain undoubtedly increase the risk of patient morbidity and mortality.

Besides the physiologic effects of inadequately managed postoperative pain, a financial burden is also placed on the patient and hospital by causing prolonged stays in the post anesthesia care unit (PACU) or hospital (Chung, Ritchie, & Su, 1997; Michaloliakou, Chung, & Sharma, 1996; Warfield & Kahn, 1995). Delayed discharge times have been associated with reduced patient satisfaction (Dalton et al. 2000).

Statement of the Problem

Postoperative pain is perceived when tissue is injured as part of surgery. Many methods for treating postoperative pain have been studied; however, it is still considered

to be poorly managed in 50% of all surgical patients and yet there is no one method of management that has proven to be completely effective (Carr & Jacox, 1992).

Previous research indicates that females may perceive pain differently than males (Otto & Dougher, 1985) and that there is a gender-related difference in response to analgesic medication (Sarton et al. 2000). Because of these gender differences in pain perception and analgesic response, a gender neutral approach to postoperative pain management may be inappropriate and inefficient. The practice of gender neutral dosing may result in poorly controlled pain for one gender and, on the other hand, increase the risk of overdose for the other gender if there truly is a difference in gender response to analgesics. Therefore, including gender as a factor for medication dosing could potentially avoid problems associated with the possibility of overmedication or undermedication.

Due to the lack of definitive methods for avoiding postoperative pain, this area of patient care remains an important area of study, especially to the practice of anesthesia. Because gender is an important aspect of pain perception that has not been studied extensively, this study focused on gender differences in postoperative pain perception.

Significance of the Problem

Postoperative pain continues to be one of the most prevalent problems in health care and it is estimated that 50% to 75% of patients have inadequate pain management despite advances in management and extensive research on the subject (Macario, Weigner, Carney, & Kim, 1999; Warfield & Kahn, 1995). Because healthcare providers statistically inadequately manage postoperative, studies must be continued to find methods for better pain management (Carr et al., 1992). Preemptive analgesia, which is administration of an analgesic prior to a painful stimulus, is a promising method of

potentially improving pain perception for postoperative patients. This concept will be explained later in further detail.

Gender differences in pain perception and the response to analgesics are currently ignored in practice standards of healthcare providers. Research providing more information on pain perception and gender differences could improve postoperative pain management. Currently, gender has consistently been disregarded in much of the literature on postoperative pain management. N-methyl-D-aspartate (NMDA) antagonists are potent analgesics which may improve pain management for patients if given preemptively in the perioperative setting. Gender differences in NMDA antagonism have been demonstrated in the animal model, but a need for further research in humans has been documented in the literature (Kavaliers, Colwell, & Choleris, 1998). If identification of a gender related difference in the response to ketamine could be found in humans, it might lead to development of safer and more efficient anesthesia dosing protocols based on patients' gender as well as their weight (the current standard).

Previous research has indicated that different analgesics do not have the same effect profile in males and females. One analgesic may have a stronger effect in males than females, another may be stronger in females than males, and another may have equal effect in both males and females. For example, ibuprofen has been shown to be more effective in males as measured by responses of subjects when subjected to painful stimulus (Walker & Carmody, 1998), while morphine has been shown to be more effective in females as measured by responses of subjects to painful stimulus while receiving an intravenous morphine infusion (Sarton et al. 2000). In both of the previous studies, pain tolerance was measured by evaluating tolerance to painful electrical stimulus administered to the subjects. Because of these differences in effect profiles, this study attempted to determine the unique effects of ketamine with respect to gender

differences and pain perception. There were no human studies found regarding gender differences in response to ketamine in the literature search for this study. However, animal studies have demonstrated that male mice are more susceptible to NMDA receptor antagonism than females (Kavaliers, Colwell & Choleris, 1998)

Theoretical Framework

Pain perception is a complex concept to define. Garrett and McShane (1999, p. 349) described pain as "a complex physiologic and psychologic reaction to potential or real tissue damage" that is also modified by experience, culture, and emotion. Otto and Dougher (1985) demonstrated that males have a higher pain threshold than females; however, the gender difference in pain threshold was not related to feelings of masculinity, femininity, or social desirability. Casey (1999) further demonstrated that there is a measurable difference between males and females in brain activity during painful stimulation. These studies provided strong objective physiological evidence supporting the hypothesis that there is a difference in pain perception between males and females.

Theories of pain perception are as equally complex as the definition. The global theory for this study was based on Melzack and Wall's gate control theory, first published in 1965. This has become the most widely accepted theory of pain mechanism and perception. Other important pain phenomena include peripheral and central sensitization. They are, however, considered subsets of the gate control theory.

Gate Control

Painful and other sensory input is carried from the periphery of the body to the spinal cord. According to the gate control theory, the dorsal horn of the spinal cord houses an anatomical region, or central gating area, that processes, modifies, and sends neural input to the brain. Within this gate, there are inhibitory interneurons and

excitatory projection neurons. Afferent nerve fibers carry sensory input, either nociceptive or nonnociceptive, from peripheral nerve receptors to the dorsal horn of the spinal cord, and converge on projection neurons in the gate. The combination of all afferent sensory input (painful or not) is integrated in the dorsal horn. The final integrated message is sent forward to the brain by projection neurons that are housed within the gate.

The "gate" opens when projection neurons are allowed to send painful information to the brain. It can only be opened when input from nociceptors overrides the activity of nonnociceptors. This gating area balances various forms of stimuli (pain, temperature, pressure, etc) that are eventually modified into one final message.

Input at the dorsal horn can be modulated by other influencing factors, such as descending tracts from the brain, certain drugs including NMDA antagonists, and cognitive and emotional input. The aspect of modulation, especially with regard to cognitive and emotional mechanisms, was ignored by prior theories used to explain pain perception and is uniquely incorporated in the gate control theory. The output at the dorsal horn is the product of various stimuli after modulation as described previously.

Central Sensitization

Within the gate control theory, certain other painful phenomena experienced by humans, specifically peripheral and central sensitization and windup must be considered. In 1966, Mendell introduced a new phenomenon of pain experience in humans known as windup. Woolf (1983) further investigated this concept in later studies. Woolf's research investigated the role of peripheral injury, such as surgical incision, in triggering enhanced excitability in the spinal cord. Woolf and Thompson (1991) specifically described a process associated with stimulation of small, unmyelinated nociceptive fibers. When stimulated in a successive manner, these small A-delta and c fibers caused a

progressive buildup of nociceptor signaling and produced a prolonged increase in the excitability of dorsal horn neurons. This hyperexcitability state changes the way pain is elicited and perceived. More recently, researchers indicate that windup is a model for a broader response called central sensitization (Li, Simone, & Larson, 1999). In the clinical setting, central sensitization is seen as an enhanced responsiveness to noxious stimuli and a reduction in the intensity of stimuli necessary to initiate pain (Woolf & Chong, 1993). These two responses, known as hyperalgesia and allodynia respectively, are components of central sensitization. Another phenomenon that is an important contributing factor to the process of pain is peripheral sensitization, which is a reduction in the threshold and widening of the receptive field of peripheral sensory pain receptors. The combination of effects within central sensitization contributes to the state of pain hypersensitivity seen postoperatively around the surgical site (Woolf & Chong, 1993).

NMDA Receptor

The NMDA receptor is a member of the glutamate receptor family and has been found to be the focal point of central sensitization. The NMDA receptor has excitatory properties that potentiate transmission of painful signals. The gating area in the dorsal horn is heavily saturated with NMDA and other receptors involved in pain processing. Tissue injury action potentials cause the release of excitatory amino acids and neuropeptides that act directly and indirectly to stimulate these receptors. Peripheral sensors send painful and non-painful signals to the dorsal horn of the spinal cord, which contains the gating area. Afferent signals are modulated within the dorsal horn and transmitted to higher perceptive areas. Once the chemical mediators activate the receptor, the NMDA receptor not only transmits pain within the dorsal horn; it also promotes enhanced excitability. Therefore the basis for pain perception is illustrated by the theoretical framework in Figure 1.

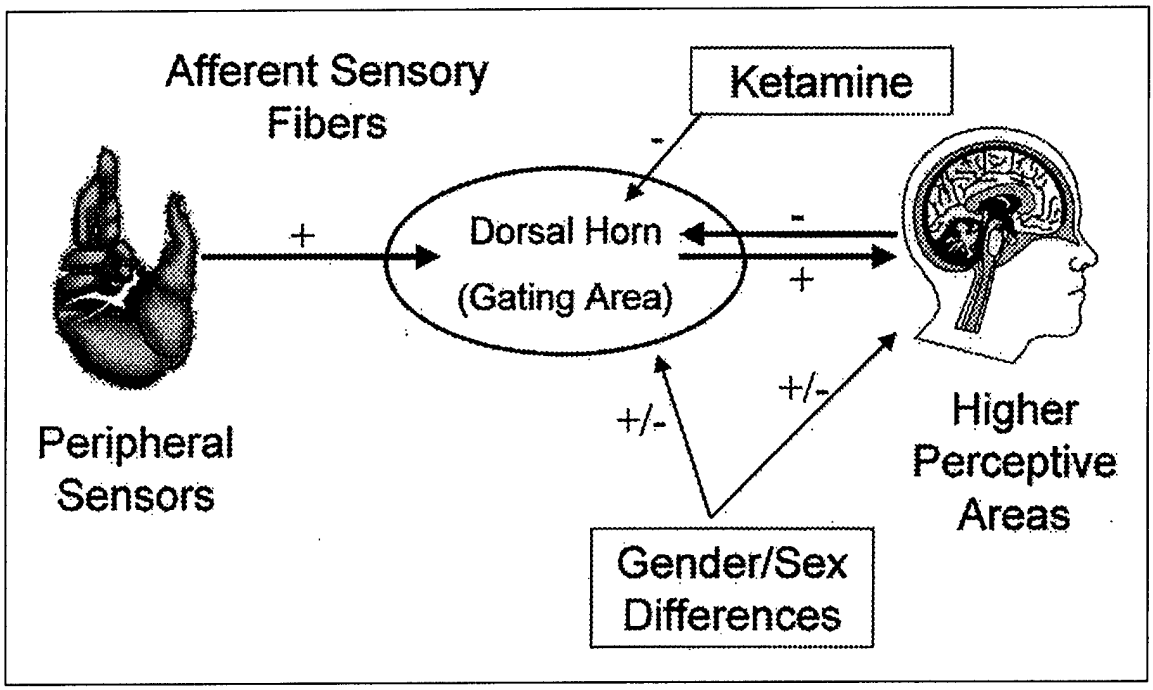

Figure 1. Conceptual Model based on the Gate Control Theory by Melzak and Wall (1965).

Ketamine

Ketamine is a noncompetitive NMDA antagonist structurally similar to phencyclidine. It has potent analgesic properties at subanesthetic concentrations. Ketamine inhibits the NMDA receptor by noncompetitive antagonism at the calcium pore on the receptor and by interacting with the phencyclidine-binding receptor site. Therefore, ketamine decreases pain signal transmission by inhibiting the NMDA receptor from participating in the pain transmission process. Ketamine works specifically at the calcium pore of the NMDA receptor and inhibits calcium influx, which in turn keeps the receptor from reaching the threshold for depolarization. If the receptor is not allowed to reach threshold, an action potential does not occur and neural transmission does not occur. Analgesia is primarily mediated by action in the limbic system and the thalamus in the brain, and both of these areas are responsible for interpretation and perception of painful stimuli.

Purpose

The purpose of this study was to compare gender differences in the effects of preemptive ketamine on perceived pain in males and females undergoing select ENT surgical procedures. For subjects who did not receive ketamine, this study allowed comparison of male and female pain levels after surgery. Finally, this study provided information about the effects of giving ketamine preemptively to surgical patients.

Definition of Terms

Pain. Conceptual definition: According to the American Pain Society (1999), pain is a physical and sensory process that occurs after an injury to the body and usually disappears when the bodily injury heals. It is often, but not always, accompanied by objective physiologic changes due to autonomic reflexes. Operational definition: The level of pain perceived as measured by the eleven point numeric reporting scale (NRS)

and the total consumption of pain medication consumed by each subject during the data collection period.

Postoperative. Conceptual definition: The recovery period after a surgery is finished. Operational definition: The period immediately following surgical closure of the operative site and emergence from anesthesia.

Preemptive analgesia. Conceptual definition: "An antinociceptive treatment before tissue injury that prevents the establishment of the altered central nociception processing that amplifies postoperative pain" (Ching-Tang et al., 1999, p. 1331). Operational definition: The preemptive administration of ketamine as defined below.

Preemptive ketamine. Conceptual definition: Administration of ketamine before the occurrence of nociceptive input to prevent sensitization and thereby decrease the duration and intensity of pain following surgery (Adam et al., 1999). Operational definition: The intravenous administration of ketamine, 0.1 milligrams per kilogram (mg/kg), to each patient immediately following the delivery of the anesthetic induction agent and prior to surgical incision.

Tonsillectomy and adenoidectomy (T&A). Conceptual definition: Surgical removal of the tonsils and adenoids (Joseph, 1998). Operational definition: Subjects diagnosed and scheduled for removal of the tonsils and adenoids by ENT surgeons.

Uvulopalatopharyngoplasty (UPPP). Conceptual definition: A surgical procedure for the correction of anatomical abnormalities associated with obstructive sleep apnea and excessive snoring caused from redundant oropharyngeal tissue (Fujita, Conway, Zorick, & Roth, 1981). Operational definition: Subjects diagnosed and scheduled for corrective surgery for the treatment of obstructive sleep apnea by ENT surgeons.

Hypotheses

1. There is a difference in the level of postoperative pain perceived by females undergoing select ENT procedures who receive preemptive ketamine as compared to males undergoing select ENT procedures who receive preemptive ketamine.
2. There is a difference in the level of postoperative pain perceived by females undergoing select ENT procedures who do not receive preemptive ketamine as compared to males.
3. There is a difference in the level of postoperative pain perceived by females and males undergoing select ENT procedures who receive preemptive ketamine as compared to females and males who do not receive preemptive ketamine.

Assumptions

Below is a list of assumptions that were made for this study.

1. Surgical ENT procedures cause postoperative pain at the surgical site.
2. Pain is a measurable phenomenon.
3. Patients will report their level of pain relative to their perceived level of pain.
4. The level of noxious stimuli will be similar among the selected ENT procedures.

Limitations

Below is a list of assumptions that were made for this study.

1. Because the study participants were drawn as a convenience sample from a large military medical center, the ability to generalize the findings from the study to the general population was limited.
2. The study was recruited from only patients undergoing select ENT procedures.
3. There was a standard plan for postoperative analgesics, however, some subjects were given other analgesics while in the PACU depending on their need. Therefore, a

morphine equivalency table was used to determine the total amount of opioid used during and after surgery.

Summary

Inadequately treated, postoperative pain can have multiple adverse physiologic and emotional effects which lead to decreased patient satisfaction, increased cost of care, and increased morbidity and mortality. Many methods of managing postoperative pain have been studied, but postoperative pain management is still inefficient. Preemptive analgesia offers the advantage of administering an analgesic prior to the infliction of noxious stimuli so that less painful stimulation is perceived

The gate control theory proposed by Melzack and Wall is a widely used and accepted explanation of pain transmission and modulation in the dorsal horn of the spinal cord. Research describing other pain-related phenomena within the dorsal horn has resulted in the inclusion of central sensitization and peripheral sensitization when considering the gate control theory and the mechanism and perception of pain. Ketamine, which is classified as an NMDA antagonist, was the drug selected as a preemptive analgesic in this study. The NMDA receptor has been implicated in the initiation of a heightened pain response. Antagonism of the NMDA receptor prior to nociceptive stimulation has been shown to inhibit pain processing.

Studies have shown that males and females perceive pain differently, with pain perception being higher while pain thresholds are lower in females as compared to males. Males and females also exhibit a gender-based difference in response to analgesics. While the amount of human studies is extremely limited, animal studies support a gender difference in NMDA receptor activity (Kavaliers, Colwell, & Choleris, 1998); however,

there have not been any published studies that have investigated the possibility of a gender difference in humans.

The purpose of this study, therefore, was to determine if there was a gender difference between male and female patients undergoing select ENT procedures in the effect of preemptively administered ketamine on the perception of postoperative pain.

In summary, a greater understanding of gender differences and postoperative pain perception, in response to ketamine, will allow anesthesia practitioners to formulate safer and more effective postoperative pain management plans. Additionally, patients may demonstrate greater satisfaction and benefit from reduced costs if less postoperative complications and decreased morbidity and mortality rates can be attributed to preemptive analgesia.

CHAPTER II

Review of Relevant Literature

This chapter provides a review of the literature relevant to the goals of this study. Discussion of the literature is organized as follows: (a) the problem of pain, (b) the significance of pain, (c) the gate control theory as the basis of the theoretical framework (d) central sensitization as part of the gate control theory, (e) the N-methyl-D-aspartate (NMDA receptor), and (f) preemptive use of ketamine. Finally, a review of the literature regarding gender differences in pain perception, response to analgesics, and response to NMDA antagonism is presented.

The Problem of Pain

Studies regarding new approaches to postoperative pain management say that pain is not treated effectively (American Pain Society Quality of Care Committee, 1995). No one strategy has been identified as the most effective plan for pain control after surgery because surgeries differ, as do individuals. Researchers continue to search for more effective approaches to minimize surgical pain. Proactive pain management to keep patients as pain free as possible has been shown to decrease morbidity, length of stay, dissatisfaction, and delayed recovery. All of which are physiologic responses to pain (Pavlin et al., 1998).

Health care organizations as well as researchers have begun focusing heavily on patient perspectives regarding pain rather than relying solely on the attitudes of health care providers. Studies investigating the attitudes of patients identify pain as a major concern when undergoing surgical procedures (Macario et al., 1999; Warfield & Kahn, 1995). Patient satisfaction studies have increased in number and pain management guidelines have been developed by numerous agencies that heavily influence the practice of health care, such as the American Pain Society (APS) and the Agency for Health Care

Quality and Research (ACHPR) (American Pain Society Quality of Care Committee, 1995; Warfield & Kahn, 1995).

Pain

Pain causes physiologic outcomes that can harm and even kill patients. Severe postoperative pain has been shown to increase morbidity (Rosenberg & Kehlet, 1999). Patients in less than optimal states of health are at increased risk for morbidity and mortality and may not tolerate the physiologic stress that unnecessary postoperative pain may cause.

When a person undergoes surgery, the sympathetic nervous system initiates the stress response, which in turn, activates endocrine, metabolic and inflammatory responses (Guyton & Hall, 2000a; Guyton & Hall, 2000b). The sympathetic response causes release of catecholamines that increase heart rate, blood pressure and oxygen consumption. These responses increase the workload of the heart, which can worsen ischemia in patients who are at risk, and worsen cerebral functioning in older patients (if hypoxemia is involved) (Mangano et al., 1992; Shulman, Sandler, Bradley, Young & Brebner; 1984).

In addition to increased circulating catecholamines that occur intraoperatively, patients may not cooperate as well with recovery efforts, which increases the risk of pulmonary complications such as atelectasis and pneumonia. If postoperative pain is severe enough to compromise a patient's recovery, the patient is also probably requiring increased amounts of pain medication. High opioid requirements can depress the respiratory drive and cause inadequate breathing efforts.

The Significance of Pain

In addition to the physiologic risks, pain is obviously an undesirable consequence of surgery. Most patients accept the fact that they will experience some amount of pain

postoperatively and expect it to occur, but it remains one of their most serious concerns (Warfield & Kahn, 1995). When pain is not managed effectively, patients may become dissatisfied, which is not beneficial for the client/caregiver relationship. Anesthesia providers are responsible for being proactive and ensuring that each patient is satisfied with the care they receive. The anesthesia provider must make every possible effort effectively mange pain the patient will have after surgery. A proactive pain management approach is the best thing for the patient as well as the provider.

The Gate Control Theory and Supporting Research

Melzack and Wall's gate control theory (1965) is the cornerstone theory of pain transmission and perception. This theory explains the mechanisms by which cutaneous stimuli, descending inhibitory systems and cognitive and emotional factors may influence the transmission and perception of pain. This theory was the framework for this study because pain perception was investigated with a focus on gender differences in relationship to associated pain modulation at the dorsal horn after preemptive NMDA antagonism with the study drug. When first developed, the gate control theory was based on anatomic and physiologic principles already known to be true, and since its introduction in 1965, research has further substantiated the anatomic and physiologic principles on which it is based. The theory has also been modified and updated regarding the relationship between cognitive and psychological factors associated with modulation of stimuli (Melzack & Casey, 1968).

The dorsal horn is the location where peripheral nociceptive or pain specific fibers terminate. The substantia gelatinosa in lamina II of the dorsal horn is the actual location of the "gate". Nociceptive and nonnociceptive fibers synapse on excitatory projection (second order) neurons that relay neural input to ascending neural tracts, and the tracts terminate in the somatosensory cortex.

Information processing and modulation occurs in the dorsal horn. Information is integrated into one message and sent via the spinothalamic and other ascending nerve fiber tracts through the thalamus to the somatosensory cortex where pain is perceived. Nociceptive fibers coming from the periphery are small diameter A-δ and C-fibers. Their role is to excite projection neurons and activate or open the gate. Simultaneously, large diameter A-α and A-β nerve fibers from the periphery carry nonnociceptive input and inhibit projection neurons closing the gate. The state of the gate depends on which nerve fibers are most actively stimulating the gate.

Intense stimulation of afferent nerve fibers in the periphery near surgical incisions causes activation of central pain pathways. Tissue damage from the incision leads to the release of natural chemical mediators (to include histamine, prostaglandins, neuropeptides, and cytokines) that sensitize the peripheral tissue around the wound. This is known as peripheral sensitization. The chemical mediator induced sensory changes include an exaggerated response to noxious stimuli (hyperalgesia). Numerous studies have illustrated the occurrence of peripheral wound changes in response to tissue damage (Campbell, Meyer, & Lamotte, 1979; Raja, Campbell & Meyer, 1984; Woolf, 1983). Unfortunately, these studies did not investigate gender as a factor. An obvious weakness included the inequality of groups with respect to males and females (7:1). In addition, they tested two subjects twice to get 10 total experiments. The results were significant, but the *p* value was not consistent and ranged from .001-.01 depending on the clinical test. Although these studies had good results, the limitations support further research.

Central Sensitization

The subsequent result of the peripheral sensitization is its central effect. Woolf (1983) conducted the initial research of peripheral injury causing centrally mediated exaggerated pain perception. In this study, he identified the process of central

sensitization. To investigate this theory, Woolf used an animal model (28 decerebrated rats) in which prolonged peripheral injury was inflicted with a noxious stimulus. The observed effect was a protracted pain response with enhanced sensitivity, and increased pain from usually otherwise innocent stimuli. This pain stimulation process is similar to the stimulation during surgical procedures. The specific process of central sensitization at the cellular level was later described as nociceptive C-fiber input causing release of substance P and glutamate in the dorsal horn (Cook, Woolf, Wall & McMahon, 1987; Woolf & Thompson, 1991). These studies also used decerebrated rats with results that were significant ($p < 0.1$ and .05). The release of chemical mediators leading to the stimulation of receptors and depolarization of second order neurons in the dorsal horn was observed. Through the release of these substances and continued signal transmission from sensitized periphery, central changes were seen in the dorsal horn. These central changes were manifested by an expansion in the rats' sensory receptive field, threshold reduction of the peripheral fibers and a prolonged response to the initial stimulus.

One of the early studies to bridge the gap from an animal model to a human model for central sensitization was done by Dahl, Erichsen, Fuglsang-Fredericksen and Kehlet, (1992). They demonstrated the effect of prolonged suprathreshold stimulation in surgical patients which led to hyperexcitability of dorsal horn neurons. The investigators hypothesized that if afferent input could be eliminated or reduced, neuronal hyperexcitability could be suppressed. The results were somewhat limited due to the skewed gender representation and treatment methods. The test group subjects were all female, while the control group subjects were male and female leading to mismatched composition of study groups for comparison. In addition, the p values varied from .006-.04 for significance.

NMDA Receptor

The key receptor identified in central gating area of the dorsal horn is the NMDA receptor. Watkins and Cheah (1965) first studied the unique properties of this receptor. Watkins' research spanned many years and culminated in a published summary of the research on the NMDA receptor and other excitatory amino acid receptors (Watkins, Davies, Evans, & Francis, 1981). The uniqueness of the NMDA receptor lies in its property of being the only known voltage and ligand gated channel. Under normal conditions, the NMDA receptor is blocked by a Magnesium (Mg^{2+}) ion, which inhibits depolarization (Mayer, Westbrook, & Guthrie, 1984; Novak, Bregestovski, Ascher, Herbet & Prochiant, 1984). These animal studies were conducted using prepared spinal neurons in Mg^{2+} free mediums. The results demonstrated less resistance of the neurons to depolarization in these preparations.

In humans, a certain amount of mediators must be released to remove the Mg^{2+} block and allow the influx of ions to depolarize the receptor. Continued release of chemical mediators and an intense barrage of noxious stimuli in the dorsal horn displace the Mg^{2+} block from the NMDA receptor. Once the Mg^{2+} block is displaced, the receptor is easily depolarized and continues to transmit nociceptive information. Thus, the hyperexcitability state associated with the process of central sensitization not only initially activates the NMDA receptor, but also helps to maintain exaggerated pain perception.

Preemptive Analgesia

Preemptive Analgesia with Antagonism of the NMDA Receptor

Since the discovery of the NMDA receptor and its involvement in the activation of nociceptive pathways in the dorsal horn, receptor antagonists have become the subject of extensive research. Researchers hypothesize that if the NMDA receptor is prevented

from depolarization, then pain signals may not be transmitted. Clinical application of this reasoning has led to the belief that blockade of the central gating area prior to surgery should reduce the perception of pain in the postoperative period. This process is known as preemptive analgesia.

Numerous studies have been conducted in animal models to support this conceptual basis for preemptive analgesia. These studies included Davies and Lodge, (1987); Dickenson and Sullivan, (1990); Haley, Sullivan and Dickenson, (1990); and Woolf and Thompson, (1991). All of these studies used mostly male rats, a variety of antagonist (MK-801, D-CPP, dextromethorphan, and ketamine), and varying routes of administration (intravenous, intrathecal, and intraperitoneal). To date, only two studies were found which used NMDA antagonists approved for human use: dextromethorphan and ketamine. All the research in animal models showed significant results in blocking the NMDA receptor and decreasing the amount of pain perceived after noxious stimuli in the animal model. The *p* values for the cited studies ranged from .01 to .05. These studies were conducted in a similar manner using decerebrated rats.

Overwhelming evidence found in animal studies allowed researchers to begin studies of NMDA receptor antagonism in humans. One of the earliest studies of NMDA receptor antagonism in a human model was conducted by Eide, Stubhaug and Stenehjem, (1995). The results supported the animal findings that NMDA receptor blockade resulted in decreased pain perception. The study used a convenience sample of 8 males and 1 female and p value of .05. The purpose of the study was to determine the effect of a bolus-continuous infusion combination of IV ketamine, alfentanil and saline on central pain. They concluded that ketamine could block central pain after a traumatic injury. Unlike this, however, they used a continuous infusion of ketamine leading to a larger total mg/kg dose with equal gender representation. Based on the reports from 33% of

their study subjects who described feelings of "unreality," a smaller mg/kg dose without a continuous infusion was selected for use in this study.

Other studies supporting the initial findings by Eide, Stubhaug and Stenehjem (1995) that NMDA receptor blockade resulted in decreased pain perception in humans include Fu, Miguel, and Scharf (1997); Helmy and Bali (2001); Henderson, Wilson, Morrison and Withingtom (1999); and Ilkjauer, Petersen, Brennum, Werngerg and Dahl, (1996).

The major limitation in these studies, however, is that the subjects recruited were primarily male subjects with only a few female subjects. Although the results were significant and supported the theory of NMDA receptor antagonism decreasing pain perception, the ability to determine gender differences in pain perception is not possible.

Preemptive Analgesia with Ketamine Administration

Researchers have often avoided or approached ketamine very cautiously due to its known pyschomimetic side effects. Subjects have reported feelings of unreality which is comparable to an out of body experience or hallucinations (Eide, Stubhaug & Stenehjem, 1995). These effects are usually reported at higher anesthetic doses of three to five milligram per kilogram.

When psychomimetic effects have occurred in studies using ketamine for NMDA antagonism in humans, the researchers concluded the combination of larger preemptive mg/kg doses (.5 mg/kg or more) and continuous infusions leading to large total mg/kg doses (Nikolajsen, Hansen, Nielsen & Arendt-Nielsen, 1996; Park, Max, Robinoviyz, Gracely & Bennet, 1995). Effective blockade of NMDA receptors has been successful with sub-anesthetic doses as low as .1 mg/kg without any reports of pyschomimetic effects. A study by Menigaux, Guignard, Fletcher, Sessler, Dupount & Chauvin (2001) not only substantiated this, but also cited six other studies that demonstrated the absence

of side effects from low dose ketamine administration. Similar to this study, they enrolled males and females electing to undergo surgery and administered ketamine IV following there induction agent; however, the dose of ketamine was .15 mg/kg and the surgeries were orthopedic. They used a *p* value of .01 and .05 to determine significance. Additionally, other studies have demonstrated that ketamine had profound analgesic properties through actions at receptors other than the NMDA receptor, unlike dextromethorphan which seemingly lacks analgesic properties (Maurset, Hustveit, Oye, & Skoglund, 1989). As noted previously, this study and the others cited supported the use of preemptive ketamine in a low mg/kg dose range to decrease postoperative pain perception and avoid undesired psychomimetic effects.

Gender Differences

As research attention became focused on the gender differences in pain and treatment of pain, evidence was found to support three factors pertinent to this study. First, males and females do not perceive pain to the same degree (Lester, Lefebvre, & Keefe, 1994; Myers, Robinson, Riley, & Scheffield, 2001; Otto & Dougher, 1985; Ratka & Simpkins, 1991; Walker & Carmody, 1998). Second, males and females respond differently to analgesic medication (Cicero, Nock, & Meyer, 1996; Sarton et al., 2000). Third, a gender difference has been observed in the activity of the NMDA receptor (Kavaliers, Colwell, & Choleris, 1998; Lipa & Kavaliers, 1990; Standley, Mason, & Cotton, 1995). Multiple theories have been proposed for these differences between males and females in pain perception and treatment including socialization and hormone differences.

Gender Difference in Pain Perception

Otto and Dougher (1985) investigated the difference in pain perception between males and females and the influence of measured levels of masculinity and femininity

and social desirability. Forty male and 40 female university students were used as the subjects of the study. The age range of the subjects was 18 to 55 years with mean ages of 22.2 years for the males and 24.9 years for the females. At the beginning of the study, all subjects completed the Bem Sex-Role Inventory and the Marlow-Crowne Social Desirability Scale. A focal pain stimulator was then used to administer a painful stimulus to the middle finger of each subject. A seven point Likert scale was used to measure the reported pain intensity by each subject. After analysis of the data, it was found that the pain threshold in males was higher than females. They concluded that the gender of the subjects could be used as a strong predictor of pain tolerance ($p<.02$), but neither masuclinity-feminity nor social desirability scores could be used to predict pain tolerance to a significant degree. On further analysis of the findings in respect to the gender of the experimenters, they also concluded that the gender of the experimenter did not have any significant effect on the data obtained.

Myers, Robinson, Riley, and Scheffield (2001) also investigated the effect of gender-role socialization as a possible explanation for gender difference in pain perception. The study sample was comprised of 54 male and 50 female graduate university students. The age range was 18 to 30 years, with a mean age of 22.4 years ± 2.98. As in the Otto and Dougher (1985) study, the subjects completed the Bem Sex Role Inventory prior to the beginning of the study. Painful stimulus was administered by having the subject immerse his or her hand to the level of the wrist in a container of ice-cold water. The results of the study supported the findings of Otto and Dougher in that the study indicated males had a higher pain threshold than females ($p = .01$), and sex-role scores did not explain the gender difference in pain perception ($p = .08$).

Walker & Carmody (1998) also investigated the gender difference in pain perception. The study sample was comprised of 10 male and 10 female patients with an

age range of 18-30 years. Prior to the study, each subject underwent a thorough medical examination to ensure he or she was healthy and pain free. Strict control measures were used to ensure as much equality among the subjects as possible. These control measures included requesting each subject to have at least eight hours of sleep the night before the study; not use alcohol, caffeine, and analgesic drugs for 24 hours before the day of the study; and to have a light carbohydrate breakfast two hours prior to the study. Temperature and sound level of the study area were controlled. During the study, subjects were either given 800 mg of ibuprofen (the experiment group) or a matched placebo (the control group). Pain stimulation was administered to each subject via electrodes, which were placed on the subject's earlobe. Analysis of the obtained data indicated the male subjects had a higher pain threshold than the female subjects prior to receiving the ibuprofen ($p < .05$).

Support for the theory of a hormonal component in the gender difference in pain perception was presented in a study by Ratka and Simpkins (1991). In this study, ovariectomized female Sprague-Dawley rats were implanted with pellets composed of cholesterol (control group), 0.5% or 5% estradiol, or 10% or 75% progesterone. Latency to lick the front paws was measured on a hot plate to assess reaction to nociceptive stimulus. Nociceptive stimulus was administered before and after the rats were administered 5 mg/kg of morphine sulfate. The rats treated with the estradiol pellets showed increased sensitivity to the thermal stimulus and decreased antinociceptive effect of morphine. The rats treated with the progesterone pellets also showed increased sensitivity to the thermal stimulus and decreased antinociceptive effect of morphine. They concluded the female hormones, estradiol and progesterone, may be a contributing factor in the gender difference in pain perception. Additionally, these results provided

evidence that the female hormones may also play a role in the gender difference in response to morphine.

In another study using undergraduate university students, Lester, Lefebvre, and Keefe (1994) performed a two-part study to investigate the influence of gender and family pain history on complaints of pain and how pain interferes with activity in young adults. Two hundred fifty two college students comprised the sample for the first part of the study, and 206 college students comprised the sample for the second part of the study. The age range of the subjects for both parts of the study was 17 to 30 years with a median age of 18 for both sample groups. Data for both parts of the study was collected by having the subjects' complete questionnaires about demographic information, student pain history, family pain history, pain intensity, pain status, pain location, and pain related activity interference. The main finding of the study, which is relevant to the subject of this study, is that the female subjects were found to report a greater number of sites of pain than the male subjects.

Gender Differences in Response to Analgesics

Cicero, Nock, and Meyer (1996) investigated gender differences in response to morphine. The study was conducted on male and female Sprague Dawley-derived rats. The rats were subjected to hot-plate, tail-flick, and abdominal-constriction tests. In the hot-plate and tail-flick tests, tests were administered and baseline data were obtained; the rats were then medicated with subcutaneous morphine and retested. For the abdominal-constriction test, the rats were pretreated with subcutaneous morphine followed by an intraperitoneal injection of either saline or 1.2% acetic acid to cause abdominal constrictions that were measured for 30 minutes. To verify that observed differences were due to gender and not a difference in the serum level of morphine, serum was collected from samples of each group to assay the morphine serum level. In each test, the

researchers found that the male rats had greater sensitivity to the antinociceptive effects of the morphine ($p < .001$), and this difference in morphine sensitivity was not related to serum level.

Sarton et al. (2000) conducted a study to determine gender difference in response to morphine in human subjects. The subjects in this study were ten male and 10 female volunteers with an age range of 21-36 years. Experimental pain was induced by transcutaneous electrical stimulation applied to the tibia of the left leg to assess baseline pain tolerance and threshold. Pain threshold was measured by having the subjects say "pain" when the electrical stimulus became painful, and pain tolerance was measured by having the subjects say "stop" when the intensity of stimulus became too painful. Following baseline measurement, each subject received an intravenous bolus dose of morphine followed by a one hour continuous intravenous morphine infusion. Pain threshold and tolerance were then reassessed using the same method used for baseline measurement. Increased pain threshold and tolerance were seen in both genders after administration of morphine. Morphine was shown to have greater potency and slower onset and offset in females than in males.

Gender Differences in the NMDA Receptor

As more research on the NMDA receptor was completed, differences were noted among males and females. Most animal studies concluded that the NMDA receptor in males is more easily antagonized than in females (Kavaliers, Colwell & Choleris, 1998; Lipa & Kavaliers, 1990; Standley, Mason, & Cotton, 1995). One study did not support these findings (Auer, 1996). All the studies were done in non-human subjects, administered an unapproved for human use NMDA antagonist, and were not designed to specifically look at pain perception differences. To date, no human studies have been

completed comparing pain perception and gender differences using an NMDA antagonist.

Summary

Pain is a major concern among patients undergoing surgery. While a proactive approach to treating pain to prevent the psychological and physiological adverse effects of pain would seem prudent, the multiple studies performed investigating various pain treatment modalities have not shown one modality to be more effective than another. As pain treatment has evolved, the focus has shifted from the health care providers view of pain to more on the patient's view of pain, and pain management guidelines have been developed by various national organizations. Severe postoperative pain has been demonstrated to increase morbidity and mortality by increasing demand on the cardiovascular system and impinging on pulmonary function. Furthermore, severe postoperative pain requires increased opioid consumption treat the pain. This increased opioid consumption places the patient at risk for life threatening respiratory depression. The adverse effects of postoperative pain can lead to increased required care for the patient and increased length of hospital stay. Increases in required care and length of stay results in increased cost of care of the patient.

The Gate Control theory by Melzak and Wall is a model for pain transmission and modulation at the level of the spinal cord. The gating area in the dorsal horn of the spinal cord contains NMDA receptors that, when stimulated, lead to increased perception of pain. When NMDA receptors are antagonized prior to painful stimulation, pain transmission is reduced and less pain is perceived.

Preemptive analgesia is a proactive approach to treating pain. The premise behind preemptive analgesia is that administering analgesics prior to initiation of painful stimulus will result in decreased transmission and perception of pain resulting in

decreased requirement for analgesics. Currently, ketamine and dextromethorphan are the only NMDA antagonists approved for human use, and both have been shown to be effective in the animal model as preemptive analgesics. While both medications have NMDA antagonist action, only ketamine has the added benefit of analgesic action. Researchers have taken a cautious approach to ketamine because of its possible psychomimetic side effects; however, sub-anesthetic doses of ketamine as low as .1 mg/kg have been used to effectively block NMDA receptor activity without incidence of psychomimetic effects.

As research in pain perception and pain management has progressed, attention has become focused on possible gender differences between males and females in pain perception and response to analgesics. Thus far, evidence supports a gender difference in pain perception between males and females, with males having a higher pain tolerance than females. Evidence supporting a gender difference in response to analgesics also exists; however, not all analgesics have shown the same effects in genders. For example, ibuprofen has a greater effect in males while morphine has a greater effect in females. The reason for gender differences in pain perception and analgesic response is not yet fully understood, but hormonal influences seem to be a contributing factor. While ketamine has been studied in the human model for effectiveness, only animal model studies have been conducted to evaluate gender differences in the action of ketamine.

CHAPTER III

Methodology

This chapter describes several aspects of this study to include population, sample, setting, instrumentation, procedure for data collection, and methods that were employed for the protection of human subjects. The purpose of this study was to compare the gender differences in perceived pain following preemptive ketamine in patients undergoing selected ear, nose, and throat (ENT) surgery specifically, uvulopalatopharyngoplasty (UPPP), tonsillectomy with adenoidectomy (T & A), tonsillectomy, and adenoidectomy (select ENT procedures).

Population, Sample, and Setting

The subjects were selected from a convenience sample of male and female patients scheduled to undergo select ENT procedures. The population was recruited from a 170 bed major military medical center located in the Pacific Northwest. This facility provided all major surgical services for eligible beneficiaries in the geographical area. Beneficiaries included active-duty military and their family members, military retirees and their family members, Department of Defense, United States Public Health Service, and Veterans Affairs (VA) eligible patients.

Inclusion criteria consisted of (a) males and females over 18 years of age, (b) physical status I or II, and (c) scheduled for any of the above mentioned surgical ENT procedures. Exclusion criteria included (a) history of psychiatric disorders; (b) long term use of opioids, benzodiazepines, nonsteroidal anti-inflammatory drugs, anti-depressant, and herbal supplements; (c) history of chronic pain; (d) history of seizures; and (e) allergy to any study medications. The standard of care at the facility where the study was conducted was for any female with the potential for pregnancy to have a beta-HCG test for pregnancy as part of the preoperative evaluation. Pregnancy was ruled out prior to

approaching subjects to participate in the study. Subjects enrolled in the study who experienced significant intraoperative events or who experienced postoperative complications that resulted in a second operation during the 24 hour data collection period were excluded from the study.

Four similar studies (Andersen et al., 1996; Helmy & Bali, 2001; Menigaux et al., 2001; Roytblat et al, 1993) from the review of the literature used an NMDA antagonist to reduce post operative pain perception. These studies were used to estimate the effect size for this study. The effect size was calculated based on Cohen's mathematical effect size calculator equation (1988). The effect sizes from these studies ranged from a medium effect size of .32 to a large effect size of 15.36. The average effect size for all four studies was large, however none of them were designed to investigate gender differences, so a more conservative medium effect size of .35 was most appropriate for this study.

Using an alpha of .05, a power of .80 and an effect size of .35, a total of 68 subjects were required for this study. Using a 10% attrition rate, the final sample size was calculated at 76 subjects.

Instrumentation

Numeric Rating Scale

The eleven point numeric rating scale (NRS) was used to evaluate pain in the postoperative period with zero representing absolutely no pain and ten representing the worst pain imaginable. The NRS, a verbal scale, was selected instead of the visual analog scale (VAS) because subjects were assessed for pain immediately on arrival to the post-anesthesia care unit (PACU). It was felt that subjects would perform better on the verbal scale in the initial recovery period, rather than having to physically manipulate the VAS. Additionally, the PACU nurses were accustomed to performing and recording these measures on a regular basis as part of the standard of care.

Prior to beginning the study, a meeting was held to discuss the NRS with the PACU nurses to ensure that the tool was used in the same manner as the investigators. A teaching tool was provided (Appendix D) for investigators and PACU nurses to use as a guide when teaching subjects how to rate pain levels. Subjects were taught in the same manner, to strengthen interrater reliability

The NRS is commonly used for assessing pain and has been found by some researchers to be just as predictive of pain intensity as the VAS with a correlation of .84 (Duncan, Bushnell, and Lavigne, 1989). Paice & Cohen (1997) demonstrated a correlation of .85 between the NRS and VAS which further indicates the two scales are equally predictive of pain intensity.

Following surgery, subjects rated their perceptions of pain using the NRS at the following five data points: on arrival to the PACU and at the first, fourth, twelfth and twenty-fourth hours following the arrival time to PACU. If subjects went home, discharge teaching included a review of the NRS and a take home questionnaire for recording pain scores and analgesics consumed. A follow-up telephone interview was done on postoperative day one to assess the subject's perioperative experience and offer assistance with the take home questionnaire when necessary. When the subjects were admitted for overnight observation, the data points remained the same and the nurse who took care of the patient on the ward assessed the pain scores at the appropriate times and recorded the data accordingly. The data collected over the telephone was helpful because many questionnaires were never mailed back.

Data Collection

The data collected during this study consisted of demographic information, specifically gender, age, height, weight, body mass index and ethnicity. Intraoperative medications used as indicated on the standard anesthetic plan in Appendix C were

recorded and the total intraoperative opioid dose, which was fentanyl in this study, was recorded. The exact time of ketamine or placebo administration was recorded. Additionally, the times of induction, intubation, surgical incision, surgical duration, extubation and admission to the post anesthesia recovery unit were recorded by the anesthesia provider. Postoperatively there were five data points for NRS scores as discussed previously along with the time in minutes to first analgesic request and the total amount of analgesics consumed within the data collection period after surgery.

Procedure for Data Collection

Subjects were recruited with the help of the Ear, Nose and Throat (ENT) clinic staff who provided written information about the study and its purpose along with consent forms. Researchers contacted potential subjects by telephone or while in the Surgical Services Center (SSC) for preoperative interviews to discuss the information the subject had been provided with and answer questions about the study. Written consent was obtained either in the SSC or on the day of surgery.

After informed consent was obtained, the subjects were randomly assigned to either a treatment or placebo group using a table using a table developed by the study's statistician. In order to ensure double blinding of the research team and subjects, a staff anesthetist who was not part of the research team used the same table to prepare either ketamine or normal saline for each subject prior to surgery. The subject's anesthesia provider was given this syringe, labeled "study drug," prior to surgery. The staff anesthetist who prepared the syringe contents kept the only log linking the randomized treatment to each subject's identification number. The anesthetist was readily available to provide this information if necessary. When the study was completed, this link was destroyed.

Data collection was performed using the data collection tool in Appendix D. A standard anesthetic plan was followed as provided in Appendix C. Once the standard preoperative medications were given, the subject was taken to the operating room where he or she was induced according to the anesthetic protocol. Ketamine, (0.1 mg/kg) or normal saline in equal volume was administered prior to intubation and surgical incision. When the surgery was complete, the subjects were admitted to the post anesthesia recovery unit (PACU) where NRS scores were recorded at the appropriate data points. Additionally the time in minutes to first analgesic request (TFA) was recorded along with the total dose of postoperative analgesics provided while in the PACU. If the subject was discharged home within the 24 hour period, he or she recorded pain scores at the appropriate data points, and all pain medications taken in that period. If the subject was admitted to the hospital following surgery, the subject's nurse recorded the same information on the data collection form. A standard protocol was used to manage postoperative pain while in the PACU and also while at home as shown in Appendix C. On postoperative day one, the subjects were contacted by telephone to discuss the postoperative experience and allowed to ask questions regarding the take home questionnaire.

Protection of Human Subjects

As stated previously, subjects were given time to review written information and consent forms and ask questions in the ENT clinic, the SSC or over the telephone prior to giving informed consent. Informed consent was obtained from each subject after a thorough explanation of the study. After counseling, subjects were asked to verbally express their understanding of the study and its purpose. The subjects were counseled of the right to withdraw from the study at any time. The subjects were ensured that they

would receive the same standard of care as other patients regardless of participation in the study.

The risks and possible benefits of participation as outlined in the consent form (Appendix B) were clearly explained prior to surgery. Risks discussed included the potential side effects of the medication as outlined in the consent form.

Confidentiality was maintained by assigning each subject an identification number, which was used on all of the study material except the consent forms. Only the primary and associate investigators had access to a logbook that contained the link to the subjects' names and identification numbers. This logbook was kept under double lock. The signed consent forms were also kept separately under double lock. The staff anesthetist who was not part of the research team kept the log that contained the randomized treatment link to the subject's identification number.

Only the aggregate data collected in the study was reported. Subjects, who desired information about the results of the study, were told they could request a copy of the study summary to be mailed to them.

Study Design

This was a prospective, double blind, gender stratified quasi-experimental study with a 2 x 2 factorial design. The subjects and the investigators were blinded to the treatment received. The subjects were recruited from a convenience sample rather than the entire population, which does not allow for true random selection, thus the design is quasi-experimental (Polit and Hungler, 1999a). Randomizing subjects to a control or comparison group attempted to keep the experiences of the two groups as identical as possible, except that the experimental group was exposed to the treatment ketamine. Changes that were seen between the groups could then be safely attributed to the treatment received. Stratification of the subjects subdivided the study groups by gender

so that this attribute could be looked at specifically. Differences in postoperative pain scores in the strata could then be compared specifically by gender. Stratification of sampling decreases sample error, increases power, and decreases the data collection time (Polit and Hungler, 1999b).

Summary

The subjects for this study were physical status one and two adult male and female patients who were scheduled for the selected ENT surgical procedures (tonsillectomy, adenoidectomy, T&A and UPPP). After informed consent was obtained, subjects were randomized into treatment and control groups. A standard anesthetic plan was followed for the administration of anesthesia and postoperative pain management. Postoperative pain perception was measured using the NRS over five data points in addition to total analgesics consumed and time to first analgesic request. Subjects were called on the first postoperative day and the same information was recorded. For data analysis, the subjects were stratified by gender and grouped accordingly by the treatment received.

CHAPTER IV

Analysis of the Data

In this chapter, the statistical data analysis of the study is presented. Specifically, sample characteristics, primary findings and secondary findings are discussed. All data analysis was done using SPSS version 10.0 for Windows with the assistance of a staff statistician.

Sample Characteristics

The subjects were selected from a convenience sample of male and female subjects electing to undergo select ear, nose, and throat (ENT) procedures (uvulopalatopharyngoplasty [UPPP], tonsillectomy with adenoidectomy [T & A], tonsillectomy, and adenoidectomy). A total of 55 subjects were approached with a total of 41 volunteering to participate in the study. During the study, an attrition rate of 7.4% was noted. The three subjects were dropped due to meeting stated exclusion criteria (1 for return to the operating room for rebleeding and two for intraoperative unusual occurrences [unrecognized difficult intubations]).

Sample characteristics for the 38 subjects (21 males, 17 females) are shown in Table 1. The demographic data included age, gender, body mass index (BMI), ASA status, and ethnicity. Sample characteristics were obtained preoperatively using the data collection tools (Appendix E). The ages of the subjects ranged from 19 to 57 with the overall mean age of 29. All subjects were active duty military or military beneficiaries. The overall BMI range was from 18 to 41 with a mean BMI of 26.8.

Table 1

Demographics

	Frequency	Percent
Male	21	55.3
Female	17	44.7
ASA I	16	42.1
ASA II	22	57.9
African American	4	10.5
Hispanic	3	7.9
Asian	2	5.3
White of Non-Hispanic descent	29	76.3

Note: Percent based on 38 total subjects.

Using an independent samples *T*-test difference between group means were analyzed and no significant differences were found in relationship to age ($t = .35$, $df = 33.93$, $p = .73$) and BMI ($t = .24$, $df = 22.34$, $p = .82$) (see Table 2).

Table 2

Age and BMI Values by Treatment Groups

Treatment	Gender		AGE	BMI
Ketamine	Male (*n*=10)	*M*	30.00	26.60
		SD	12.61	3.06
	Female (*n*=7)	*M*	31.29	24.57
		SD	7.52	2.99
	Total (*n*=17)	*M*	30.53	25.76
		SD	10.54	3.11
Saline	Male (*n*=11)	*M*	29.36	27.27
		SD	12.27	3.69
		N	10	10
	Female (*n*=10)	*M*	26.60	27.90
		SD	7.25	8.31
		N	21	21
	Total (*n*=21)	*M*	28.05	27.57
		SD	10.04	6.16

Primary Findings

This study was designed to compare gender differences in the effects of preemptive ketamine on perceived pain in males and females undergoing selected ENT surgical procedures. For subjects who did not receive ketamine, this study allowed comparison of male and female pain levels after surgery. Finally, this study provided information about the effects of giving ketamine preemptively to surgical patients. For

the above comparisons, 3 hypotheses were proposed to investigate.

To investigate these hypotheses, the data was analyzed using an independent sample *t*-test and a repeated measures analysis of variance (ANOVA). The *t*-test is a simple parametric test to assess differences between two group means. This test was used to analyze the time to first analgesic request (TFA) and total opioid consumption. Like the *t*-test, the ANOVA is used to test the differences between means. Unlike a *t*-test, the ANOVA has the ability to test the means of 3 or more groups and is a between subjects analysis. With a repeated measure ANOVA, an analysis of 3 or more measures on the same dependant variable in a longitudinal fashion is possible. Also the variation between treatment groups is analyzed against the variation within groups. From this an *F* ratio is yielded and allows for the establishment of the probability that the treatment resulted in the difference measured. For this study, ANOVA was used to analyze postoperative pain (NRS scores).

Hypothesis 1: There is a gender difference in the level of postoperative pain perceived by females undergoing select Ear, Nose, and Throat (ENT) procedures who receive preemptive ketamine as compared to males undergoing select ENT procedures who receive preemptive ketamine.

Using the repeated measures ANOVA, there was no significant difference in pain between the two genders based on the self reported pain using the Numeric Rating Scale (NRS) scores. Additionally, the independent samples t-test showed no significant difference in time to first analgesic request (TFA) between the two genders. Finally, no significant difference was detected for total opioid consumed postoperatively either (see Table 3). For this hypothesis, the null hypothesis was supported.

Table 3

Statistical Values for Groups that Received Preemptive Ketamine: Male vs. Female

	Statistic	*df*	*p*
NRS Scores[a]	.09	1, 14	.77
TFA[b]	- .11	15	.91
Total Opioid Consumption[b]	1.13	14	.28

Note: [a]A repeated measures ANOVA was used for NRS scores using the *F* statistic. [b]An independent T-test was used for TFA and total opioid consumption using the *T* statistic. A p value < .05 was considered significant.

Hypothesis 2: There is a difference in the level of postoperative pain perceived by females undergoing select ENT procedures who do not receive preemptive ketamine as compared to males.

Using a repeated measures ANOVA, no significant difference in pain perception between the two genders based on the NRS scores was shown. An independent samples *t*-test showed no significant difference in TFA between males and females. Additionally, no significant difference was detected for total opioid consumed postoperatively either (see Table 4). The null hypothesis was supported.

Table 4

Statistical Values for Groups that Did Not Receive Preemptive Ketamine: Male vs. Female

	Statistic	***df***	***p***
NRS Scores[a]	.001	1, 18	.98
TFA[b]	- .11	15	.91
Total Opioid Consumption[b]	1.13	14	.28

Note: [a]A repeated measures ANOVA was used for NRS scores using the *F* statistic. [b]An independent T-test was used for TFA and total opioid consumption using the *T* statistic. A p value < .05 was considered significant.

Hypothesis 3: There is a difference in the level of postoperative pain perceived by females and males undergoing select ENT procedures who receive preemptive ketamine as compared to females and males who do not receive preemptive ketamine.

Using the same repeated measures ANOVA, there was no significant difference in pain perception between the ketamine and placebo groups based on the NRS scores. An independent samples t-test showed no significant difference in TFA between the ketamine and saline groups. Lastly, no significant difference was detected for total opioid consumed postoperatively either (see table 5). The null hypothesis was supported.

Table 5

Statistical Values for Ketamine vs. Saline groups

	Statistic	*df*	*p*
NRS Scores[a]	.005	1, 34	.94
TFA[b]	.59	35	.56
Total Opioid Consumption[b]	1.02	33	.31

Note: [a]A repeated measures ANOVA was used for NRS scores using the *F* statistic. [b]An independent T-test was used for TFA and total opioid consumption using the *T* statistic. A p value < .05 was considered significant.

Secondary Findings

Experts in the clinical area at the study site were of the opinion that our selected surgical population would have large differences in pain scores and analgesic requirements. They based this difference on the incongruence in total surgical time and overall amount of tissue trauma involved in the different ENT procedures under study. For equivalent comparison, the ENT procedures were separated into Tonsils (included tonsillectomy, adenoidectomy, and T & A) and UPPP (UPPP and UPPP with tonsillectomy). The mean surgical time for the tonsils was 25.8 with a *SD* of 14.5, while for the UPPP groups had a mean of 40.4 with a *SD* of 17.1. A *t*-test was used for total surgical time, TFA and total opioid consumption, while a repeated measures ANOVA was used for the NRS pain scores analysis (see Table 6). As illustrated in table 6 and 7, there were no significant differences detected in NRS scores, total surgical time, TFA, and total opioid consumption between the Tonsils groups vs. UPPP group. In conclusion, the opinions of the clinical experts were not supported in this study.

Table 6

ANOVA Values for the NRS Scores for Comparison of T&A vs. UPPP Groups

	F	*df*	*p*
NRS Scores	.56	34	.46

Note: Total number of subjects in Tonsil group=21, Uvulopalatopharyngoplasty group=15.

Table 7

T-test Values for T&A vs. UPPP Groups Comparing Total Surgery Time, TFA and Total Opioid Consumption

	T	*df*	*p*
Total Surgical Time	.42	36	.52
TFA	.68	35	.42
Total Opioid Consumption	1.35	33	.26

Note: Total number of subjects in Tonsil group=22, uvulopalatopharyngoplasty group=15 for TFA and total surgical time; Total number of subjects in Tonsil group for total opioid consumption=21, uvulopalatopharyngoplasty group =14.

Finally, a Friedman test to rank the pain scores for each subject across the different data collection points was completed. Unlike the ANOVA for NRS scores, this test analyzed the ranked mean NRS scores across the entire sample. Results show the sum of the ranks are about equal, the value of the test statistic is 5.25 which, with $df = 2$, has a significance of .27. For an alpha = .05, this value is not statistically significant. Thus any differences in the rankings across subjects simply reflected sampling error and not any

significant differences in pain over the five data collection points (see Table 8).

Table 8

Mean Ranks Pain Scores

	Mean Score
1st Pain score	3.84
2nd Pain score	3.39
3rd Pain score	2.89
4th Pain score	3.39
5th Pain score	3.28

Note: For pain scores 1-3, the N=38. For pain scores 4 and 5, the N=36.

Summary

In review of our data, 41 total subjects were enrolled with 38 in the final analysis. Three subjects were dropped in accordance with stated exclusion criteria (2 difficult intubations and 1 return the operating room in the first 24 hours). Analysis of the demographic data revealed no significant difference in the subjects. Following thorough analysis with the independent sample *t*-test and repeated measures ANOVA, the null hypothesis was supported for each of the hypotheses in our primary analysis. No significant gender difference was shown for postoperative pain perception following preemptive ketamine or preemptive saline, and no significant difference was shown in postoperative pain perception between subjects who received preemptive ketamine and those who received preemptive saline. In an effort to validate the opinions of clinical experts, a secondary analysis was done to test for a significant difference between the two surgical groups. Contrary to expert clinical opinion, the results of the secondary analysis

did not support a significant difference between the Tonsil surgical group and the UPPP surgical group in terms of surgical time and postoperative pain perception. A final analysis of pain scores was done using the Friedman test to analyze the ranked mean NRS scores across the entire sample. This analysis revealed no significant difference in the mean scores and thus pain perception across the five data collection points.

CHAPTER V

Discussion, Conclusions, Implications, and Recommendations

Postoperative pain is perceived as a result of tissue injury during surgery. While there are many methods for treating postoperative pain, it is still considered poorly managed. Furthermore, research supports a gender difference in the perception of pain (Otto & Dougher, 1985) and effectiveness of analgesics (Sarton et al., 2000). Because of the gender differences in pain perception and analgesic effectiveness, a gender neutral approach to postoperative pain management may be inefficient. Other analgesics, such as morphine and ibuprofen, have been studied in the human model to determine the presence of a gender difference; however, no human studies investigating a gender difference with ketamine have been published to date. The purpose of this study was to determine if a gender difference in the effectiveness of ketamine was present.

This chapter begins with a discussion of the study to include the conceptual framework used to guide the study design, the primary and secondary findings that came about as a result of the study, and the strengths and weaknesses of the study. Next will be discussed the conclusions of the study followed implications of the study results and conclusions. Recommendations for future research and anesthetic practice will then be discussed. Finally, a summary of the chapter will be given.

Discussion

Conceptual Framework

The conceptual framework for this study was based on the gate control theory by Melzak and Wall (1965). According to the gate control theory, sensory input is transmitted from peripheral receptors along afferent nerve fibers to the dorsal horn of the spinal cord. Within the dorsal horn is a central gating area that processes and relays input from the periphery to the brain. The gating area contains both inhibitory interneurons

and excitatory projection neurons. When painful signals from the periphery override nonpainful signals, the "gate" is opened, and pain signals are transmitted to the brain. The N-methyl-D-aspartate (NMDA) receptor in the dorsal horn is one of the modulators of the gating area. By antagonizing the NMDA receptor with drugs such as ketamine, pain signal transmission at the level of the gating area is reduced, thereby reducing pain signals transmitted to the brain.

Primary Findings

Pain perception was evaluated using three different methods. The first was having the subjects assess their pain level on a Numeric Rating Scale (NRS) at five points in time (arrival to the postanesthesia care unit (PACU), first, fourth, 12th, and 24th hours after arrival to the PACU). The second was tracking the time to first analgesic (TFA) request of each subject after arrival to the PACU. The third evaluation method was tracking the total opioid consumption of each subject during the first 24 hours after surgery. For each evaluation method, a p value of .05 or less was considered significant.

Hypothesis 1: There is a gender difference in the level of postoperative pain perceived by females undergoing select Ear, Nose, and Throat (ENT) procedures who receive preemptive ketamine as compared to males undergoing select ENT procedures who receive preemptive ketamine. When the NRS scores, TFA values, and total opioid consumption were evaluated, no significant difference was shown between females and males who receive preemptive ketamine prior to the selected ENT procedures; therefore, the first hypothesis was not supported. Considering the administration of a NMDA antagonist was intended to cause a gender difference in postoperative pain perception, it could be assumed that there is not a gender difference in NMDA antagonism in humans. Based on studies such as Kavaliers, Colwell, and Choleris (1998), males were expected to have less postoperative pain perception than females. The theoretical model for this

study also predicted a gender difference in NMDA antagonism and postoperative pain perception. The findings of this study do not support the theoretical model or most of the previous studies regarding gender differences in NMDA antagonism. However, although this study was performed with human subjects, it does support the findings of Auer (1996) that NMDA receptors in males are no more sensitive to antagonism than those in females. But these results must be viewed with caution because of the inadequate sample size obtained relative to the required sample size and the under representation of females in each group.

Hypothesis 2: There is a difference in the level of postoperative pain perceived by females undergoing select ENT procedures who do not receive preemptive ketamine as compared to males. When the NRS scores, TFA values, and total opioid consumption were evaluated, there again appeared to be no significant difference between females and males who did not receive preemptive ketamine prior to the selected ENT procedures. In other words, there is no difference between how females and males perceive postoperative pain; therefore, the second hypothesis was not supported. The theoretical model for this study predicted there would be a gender difference in the level of postoperative pain perception. Based on the results of previous studies by Meyers, Robinson, Riley, and Scheffield (2001); Otto and Dougher (1985); and Walker and Carmody (1998); males were expected to perceive postoperative pain less than females after receiving the placebo preemptively. By supporting the null hypothesis, the results of this study fail to support the theoretical model and previous gender difference pain research. However, there were only seven females in the ketamine group as compared to ten males, and the required sample size was not met; therefore, these results must also be viewed with caution.

Hypothesis 3: There is a difference in the level of postoperative pain perceived by females and males undergoing select ENT procedures who receive preemptive ketamine as compared to females and males who do not receive preemptive ketamine. When the NRS scores, TFA values, and total opioid consumption were evaluated, there again appeared to be no significant difference in the level of postoperative pain perceived by males and females who received preemptive ketamine as compared to those who did not receive preemptive ketamine. These findings indicate that administering a preemptive dose of ketamine does not decrease the amount of pain perceived postoperatively; therefore, the null hypothesis is supported and the theoretical model is not. Postoperative pain was expected to be perceived less in subjects who received the preemptive dose of ketamine than those who received placebo. These results do not support previous research regarding preemptive analgesia with ketamine. However, there are some differences between this study and previous studies regarding the ketamine dose and administration. The ketamine dose in this study was .1 mg/kg instead of the .5 mg/kg dose used by Nikolajsen, Hansen, Nielsen, and Arendt-Nielsen (1996) and Park, Max, Robinoviyz, Gracely, and Bennet (1995) or the .15 mg/kg dose used by Menigaux, Guignard, Fletcher, Sessler, Dupount & Chauvin (2001). Also, Eide, Stubhaug, and Stenehjem (1995) used a continuous infusion administration method of ketamine instead of a single bolus dose as was used in this study. It is possible that, had a larger dose of ketamine, similar to that used in previous studies, been used, a significant result in postoperative pain perception would have been seen between the ketamine group and the placebo group. However, as the administered dose of ketamine increases, so does the subjects risk of experiencing side effects of the ketamine.

Explanation of Results of Findings

For each of the hypotheses, data supports the null hypotheses. Furthermore, the

obtained data also failed to support previous studies regarding gender differences in NMDA antagonism and pain perception. The main factor that may account for this lack of support is the small sample obtained in this study. Based on an alpha of .05, power of .80, an effect size of .35, and an attrition rate of 10%, the required sample size for this study was 76. Only 41 subjects, just over half the calculated number of subjects, were recruited for this study. The randomization table used to assign subjects to either treatment or placebo groups was generated prior to initiation of the study. As subjects entered into the study, they were first stratified by gender then assigned to either the treatment or control group. By the time the 76th subject entered the study, a nearly equal number of subjects would have been in each cell of the 2 x 2 analysis grid. However, since the required number of subjects were unable to be recruited, there was an unequal distribution between the groups which may have skewed the results. The sample obtained may also not have been of sufficient size to detect the difference between the groups because as the sample size of a study decreases, the statistical power of that study also decreases. In order to reject the null hypothesis, a small sample size is sufficient if the difference to be detected is large; however, if the difference to be detected is small, then a large sample size is required.

While no one factor may have lead to the smaller than required sample size, the combination of military deployments and academic timelines of the thesis resulted in a decrease in the available population and amount of time available to conduct the study. The first reason for the small sample size was deployments of soldiers to Southwest Asia during the time the study was being conducted. The population from which the study sample was recruited were active duty military and military beneficiaries. As soldiers were deployed to Iraq, the population was diminished in two ways. First, the deployed soldiers were no longer present to be candidates for the selected ENT surgeries. Second,

when the soldiers were deployed, some of there families left the area to live with other relatives during the deployments resulting in a smaller population of military beneficiaries who would be candidates for the selected ENT surgeries.

The second reason for the smaller than required sample size is also related to military deployments to Southwest Asia. To assist in with providing medical support for the deployed soldiers, surgeons, anesthesia providers, and other operating room staff were deployed, resulting in a decrease in the availability of providers to provide the services required for the selected ENT surgeries and a decrease in the number of surgeries being performed.

A third reason for the smaller than required sample size was that the study ended before the required sample was obtained. This was because the data collection period was not able to be extended because of the academic timeline. Had either or both of the influencing factors of military deployments and the academic timeline not been present, the required sample may have been obtained and sufficient data obtained to adequately test the hypotheses.

Secondary Findings

Since the majority of the surgeries performed were tonsillectomy and adenoidectomy (T&A) and uvulopalatopharyngoplasty (UPPP), the data for the subjects who underwent these surgeries were used. First, clinical experts at the military treatment facility felt that there may have been a difference in the length of the two different procedures which might contribute to an increase in pain perception in the longer surgery. Analysis using a *T*-test, there was showed no significant difference in the length of time required to perform the two different ENT procedures. When the NRS scores for the patients undergoing T&A were compared to those who underwent UPPP using an ANOVA, there was not a significant difference in pain perception between the two

groups. To verify this result, a *T*-test was used to analyze the time to first analgesic request (TFA) and total opioid consumption between the two groups. The *T*-tests for these two criteria also showed no significant difference in pain perception.

The NRS scores of the subjects who participated in the study were analyzed using a Friedman test to determine if there was a significant difference in the level of pain perception over the data collection points. The results of the test showed no significant difference in the level of pain perception over the data points. This would indicate that the pain experienced by the subjects did not significantly vary during the first 24 hours. Most of the patients reported their pain control was at least adequate.

Strengths

As with any other study, there were strengths and weaknesses related to this study. Many of the strengths of the study are related to its design, and the limitations of the study are related to its implementation. The strengths of the study included the theoretical model and the standardized anesthetic plan, while the limitations were the population from which the subjects were recruited and the small sample size obtained.

The Gate Control Theory was initially proposed by Melzak and Wall (1965) and further investigated and supported by Melzack and Casey (1968). Woolf (1983) began research regarding central sensitization, which was further investigated and supported by Cook, Woolf, McMahon, and Wall (1987), and Woolf and Thompson (1991). These first central sensitization studies were performed in animal models, but Dahl, Erichsen, Fuglsang-Fredericksen, and Kehlet (1992) supported the central sensitization theory regarding humans. A strength of this study is that the theoretical model used was based on results of these studies as well as other studies that investigated NMDA gender differences in animals.

Another aspect of the study design that gave strength to the study was the

development of a standard anesthetic plan that was used during the study. This standard plan made the treatment of each subject as similar as possible and reduced extraneous factors that would have potentially interfered with obtaining a clear understanding of the differences between groups.

Limitations

A limitation of the study was related to the implementation of the study. The population from which the sample was drawn was active duty military and their dependents. Because of the general state of health of this population, it limits the ability to generalize the findings to the non-military population.

Another limitation of the study was the actual number of subjects who were recruited and participated in the study. The required number of subjects calculated was based on a medium effect size. Because the number of subjects who participated in the study was just over half that required, there may have actually been a difference between the groups that was not detected.

Internal Validity

Internal validity tests whether the research findings are the result of the relationship between the independent and dependant variable or whether the findings result from other factors (threats). Threats to internal validity for this study included selection, testing, and instrumentation. A selection threat occurs when individuals themselves decide whether to participate in the study. This effect promotes unequal groups. The potential selection bias for this study was related to the need to use a convenience sample of patients requiring the select ENT procedures instead of a variety of surgical patients with different surgical needs. We used stratified random assignment of subjects to avoid having unrepresentative, nonequivalent groups to reduce the risk of a

selection threat. Additionally, demographic data were collected to evaluate for significant differences among groups.

A testing threat is the effect of taking a pretest which may sensitize the subject and improve the posttest score. In our case, this effect was the repeated measurement of pain scores with the same tool. The process of having the subjects' use the same pain score test repeatedly may have influenced the data obtained from the tool. Due to the small number data points (5) and their collection within 24 hours this effect was minimal. Also, all of the data point measurements were concluded within 24 hours.

Instrumentation threats occur when different observers use different techniques to measure data points and may cause variability in measured data. This threat could have been significant in our study because data points were collected by a number of individuals: PACU nurses, ward nurses, researchers and the subjects themselves. We attempted to minimize this threat by using the NRS as the only instrument versus multiple techniques for pain measuring. In addition, it did not require any subjective evaluation by anyone other than the research subject.

External Validity

External validity addresses the problems that limit the researchers' ability to generalize the study findings to the general population. In this study, threats to external validity include the reactivity effect, single site, and selection and treatment (declination of subjects). The reactivity effect, also known as the Hawthorne effect, is the response from subjects being studied. It has been shown that this occurs when the behavior of a subject is changed because he or she is aware of being observed or studied. To minimize this effect, this study used a double-blind approach for controlling reactivity. The subjects and researchers were unaware of the treatment received. Also, by using current

ward and PACU protocols, the nursing staff cared for all the patients in the same manner regardless of their participation in the study.

The threat of selection affects external validity. Specifically, selection of subjects from a single site that cared for active duty military and military beneficiaries resulted in a younger healthy population for this research study. This study, therefore, had limited generalizability due to the single site younger and healthy population.

Conclusions

In summary, this study found no statistically significant differences between males and females whether they received ketamine or not. Because the number of subjects recruited for participation in the study was smaller than the required number, conclusions must be viewed with caution.

Unlike as has been seen in animal models, there may not be a significant difference in postoperative pain perception between males or females undergoing selected ENT surgeries when preemptively administered ketamine. However, further study must be done to support this conclusion.

There may not be a significant difference in postoperative pain perception between those who do and those who do not receive a .1 mg/kg preemptive dose of ketamine when undergoing selected ENT surgeries. Higher doses of ketamine given preemptively, however, may show a significant difference in postoperative pain perception. Additionally, since the preemptive analgesic action of ketamine takes place in the dorsal horn of the spinal cord, a significant difference in postoperative pain perception may seen in subjects undergoing surgery in an area more innervated by spinal nerves instead of cranial nerves.

There may not be a difference in the level of postoperative pain between males and females undergoing selected ENT procedures. Since gender differences in pain

perception are not fully understood further study must also be done to support this conclusion.

Contrary to expert opinion, this study did not support a significant difference in the level of postoperative pain perceived between those who undergo T&A and those who undergo UPPP. Also, the level of postoperative pain perceived does not significantly change over the first 24 hours following T&A and UPPP.

Implications for Anesthesia Practice

Based on the primary findings of this study, implications for anesthesia practice are that the current practice of weight based dosing for ketamine is sufficient, and there is no need to adjust dosing for each gender. Additionally, preemptively administering ketamine in subanesthetic doses prior to ENT surgery is not necessary as it appears not to have any significant benefit. There is also the implication that, since males and females do not appear to significantly perceive pain differently after ENT surgery, no additional considerations related to gender of the patient need to be taken when planning for postoperative analgesia. However, more research is needed in these areas.

The secondary finding that tonsillectomy and adenoidectomy (T&A) surgery does not significantly differ from uvulopalatopharyngoplasty (UPPP) in terms of surgical time and postoperative pain may implies that similar intraoperative and postoperative analgesic plans can be used for both surgeries. The other secondary finding that postoperative pain perception did not change significantly over time for the first 24 hours after surgery implies that the current regimens used for postoperative pain control for T&A and UPPP are at least adequate and do not require change.

The presented implications are based on the data obtained in this study and the results of analyzing that data. It must be reiterated, however, that, because of the small number of subjects recruited relative to the number required, this study may have lacked

adequate statistical power, and a larger difference in pain perception and analgesic use would have to have been present to correctly reject the null hypotheses. Therefore, the results of this study are not strongly supported because of the smaller than required sample size and potential for a type II error.

Recommendations for Further Research

Based on the data and results obtained from this study, a few recommendations for future research can be made. These recommendations are made for the purpose repeating this study or variations thereof.

The first recommendation is that this study be repeated with adequate sample size. While several studies have been done to investigate a gender difference in the activity of the NMDA receptor and the effectiveness of ketamine in the animal model, more research needs to be done to investigate this phenomenon in humans. Even though this study supported there is no difference, future studies with adequate sample size may be able to detect a difference.

The second recommendation is to change the study design. By using fewer variables, a smaller sample size would be required, and less factors would need to be controlled for. For example, a study could be done that compared males and females that received ketamine without a control group. The disadvantage to eliminating the control group is that there would no longer be means to verify the difference seen is because of the treatment received instead of other factors.

The third recommendation is to use only one surgical population for subject recruitment. Although the secondary findings did not support a difference in the level of postoperative pain perception between T&A and UPPP, the sample size may have been too small to detect a difference.

The fourth recommendation is that this study be repeated in surgical populations

other than ENT surgeries. Because of the innervation of oropharyngeal area, insufficient pain transmission may have been relayed through the gating area in the dorsal horn of the spinal cord for the theoretical model of this study to have been applicable to ENT surgeries. Surgeries involving areas of the body more heavily innervated by spinal nerves may be more suited to the theoretical model and design used in this study.

The final recommendation is that this study be repeated as a multicenter study that would encompass hospitals providing care to both military and civilian patients. This would allow for greater diversity of all demographic factors among the subjects resulting greater generalization of the results to the overall population and an increased ability to recruit and equal number of male and female subjects.

Summary

The perception of postoperative pain is the result of tissue injury during surgery. Using a conceptual model based on the Gate Control Theory by Melzak and Wall (1965) and studies regarding preemptive analgesia and gender differences in NMDA receptor activity, effects of analgesics, and pain perception, this study investigated three hypotheses related to effectiveness of preemptively administered ketamine vs. Placebo and gender differences in postoperative pain perception given same study drug. The primary findings supported the null hypotheses that there was no difference in the effect of preemptively administered ketamine and no gender differences in the effect of preemptively administered ketamine or in postoperative pain perception. Additionally, the secondary findings showed no difference in postoperative pain perception over the five data collection points, or a difference in postoperative pain perception between the two categories of ENT surgeries T&A or UPPP. However, the smaller than required sample number of subjects recruited for the study may not have been sufficient to provide enough statistical power to detect a difference that may have been present. While the

results of this study do not support a change in current anesthetic practice, this implication must be viewed with a critical eye given the limitations of the study. The most important recommendations to future research coming from this study are that this study should be repeated with required study numbers and changing the target population to a larger one that includes military and civilian subjects presenting for the same surgical procedure.

Preventing or minimizing postoperative pain through the use of preemptive analgesia is one of the goals of all anesthesia providers. Further studies to determine if pain management can be improved by considering gender differences continue to be a worthy endeavor.

APPENDIX A

Information Letter

Dear Ma'am or Sir,

This letter is to inform you of a scientific research study that will be conducted by the U.S. Army Graduate Program in Anesthesia Nursing at Madigan Army Medical Center. The purpose of this study is to identify differences in pain responses of females and males after surgery.

Ketamine, an anesthetic medication with pain relieving abilities, has been used in anesthesia for many years, and it will be used as the study drug. Either the study drug or normal saline (a placebo) will be given intravenously through your IV by the anesthesia provider after you are asleep and before the first surgical incision is made. A placebo is not a drug; it has no pain relieving properties. A placebo is used to compare to a drug that is being studied because it should have no effect in the study results. Differences in pain levels between males and females will be investigated during the first twenty-four hours after surgery.

If you agree to be in the study, you will be required to use a pain scale to score your pain in the first twenty-four hours after surgery. This is routine nursing practice used to assess all postoperative patients' pain. The only requirement the study places on you is to fill out a take home questionnaire to score pain in the first twenty-four hours. The questionnaire will also ask you to record the number of pain pills you take while at home. We will also ask you to mail the questionnaire back to us (in a self-addressed stamped envelope that will be provided to you).

We will also call you on the first day after surgery to offer assistance with the questionnaire and answer any questions that you might have. The questionnaire and the follow-up phone call are the only requirements placed on the subject that are not part of usual routine postoperative care.

. The use of ketamine may prolong your return to duty status for specific jobs (i.e. aviation, handling of sensitive items or material, etc); therefore, we strongly encourage participants to review specific guidelines regarding ketamine and general anesthesia with your supervisor regarding limitations or disqualification from performing your normal daily duties following your convalescent leave.

Please read the consent form you received along with this letter for more detailed information and consider your participation in this study prior to your pre-anesthetic interview scheduled in the Surgical Services Center. We will answer any further questions you may have and discuss your desire to participate in the study on the day of your appointment. Participation is absolutely voluntary. We appreciate the time you have taken to hear about our study and look forward to discussing it with you at a later date.

Our sincere thanks,

Dennis Turner, CPT, AN, Primary Investigator
CPT Robert Ladd and 1 LT Carrie Pike, Associate Investigators
U.S. Army Graduate Program in Anesthesia Nursing

APPENDIX B

Volunteer Agreement Affidavit

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25 or AR 40-38; the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority:	10 USC 3013, 44 USC 3101 and 10 USC 1071-1087
Principle Purpose:	To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purpose.
Routine Uses:	The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs, teaching, adjudication of claims, and for the mandatory reporting of medical condition as required by law. Information may be furnished to Federal, State and local agencies.
Disclosure:	The furnishing of SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ SSN _____
having full capacity to consent and having attained my _____ birthday, do hereby volunteer to participate in the research protocol **A comparison of gender differences in perceived pain following preemptive ketamine in patients undergoing selected ear, nose, and throat surgery (known hereafter as select ENT surgery)** under the direction of CPT Dennis R. Turner and supervised by the US Army Graduate Program in Anesthesia Nursing faculty conducted at Madigan Army Medical Center.

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by _____.

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. **Should any further questions arise concerning my rights study-related injury I may contact the Center Judge Advocate at Madigan Army Medical Center, (206) 968-3113.**

I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits; however, I may be required (military volunteer) or requested (civilian volunteer) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary form my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

PART B - EXPLANATION OF WHAT IS TO BE DONE

INTRODUCTION: You have been invited to participate in a clinical research study conducted at Madigan Army Medical Center because you have been scheduled for either a tonsillectomy, adenoidectomy, adenotonsillectomy (T&A), or uvulopalatopharyngoplasty (UPPP). Participation is entirely voluntary; if you decide not to participate, penalty or loss of benefits to which you are otherwise entitled will not be effected. A total of 76 patients will be enrolled in the study at Madigan Army Medical Center.

PURPOSE: The purpose of the study is to determine if there is a difference between men and women in pain perception after they have been given a drug to relieve pain before surgery and between men and women who have not been given a drug to relieve pain before surgery.

EXPLANATION: Studies have shown that preemptive analgesia (pain medication given before surgery) may decrease pain after surgery. Preemptive analgesia is the term used for giving pain medication before a painful event, such as surgery, to decrease the amount of pain a person feels after the event. The drug used in this study for preemptive analgesia is called ketamine. Ketamine is a drug that has been studied for preemptive analgesia and shown to reduce pain after surgery. It is also possible that ketamine may reduce pain differently for men than it does for women.

PROCEDURES: If you agree to participate in this study, you will be randomly assigned in one of two groups to receive the study drug. Randomization, such as a flip of a coin, makes sure that every one has an equal chance (50%) of being selected to receive the study drug. One group will receive ketamine .15 mg/kg and the other group will receive a placebo. In this study, the placebo is a salt solution that looks like the study drug, but has no known side effects. Neither you nor your

anesthetist will know which one you will get. If there is a need to know which one you got, the pharmacist will be able to immediately inform your anesthesia provider.

On the day of surgery, you will arrive at the preoperative holding area. You will be met by your anesthesia provider and your surgeon before going to the operating room to have your surgery. Once you are in the operating room, you will go to sleep for surgery as you normally would, and after you are asleep you will be given the study drug. You will not know when the drug is given and will not feel it when it is given either.

After the surgery is finished, your anesthesia provider will wake you up and take you to the recovery room. When you arrive to the recovery room, you will be asked by your nurse to rate your pain on a scale of zero to ten (10), with zero meaning absolutely no pain and ten meaning the worst pain you can imagine. This rating scale will help the nurses and investigators understand how much pain you are feeling. Even if you were not participating in the study, you would still be asked to rate and describe your pain to your nurse after surgery. Pain medication can be given to you in the recovery room if you need it.

You will be asked to rate your pain four more times over the next 24 hours after you arrive to the recovery room. Depending on the type of surgery you have, you may go home or to a patient ward after you leave the recovery room. If you stay in the hospital, your nurse or the investigators will ask for your pain scores as described above. If you go home, a survey will be sent with you that asks you to record your pain at certain times (12 and 24 hours after you arrived in the recovery room). An investigator will either visit you in your hospital room or call you at home the day after surgery. At that time, any questions you have will be answered, your surgical experience will be discussed and the investigator will assist you with the questionnaire if needed.

POTENTIAL BENEFITS: There may be no benefit to participating in this study; however, there are studies that show patients who receive ketamine before surgery may feel less pain after surgery. We hope the information learned from this study will benefit other patients with pain management after surgery.

RISKS, INCONVENIENCES, AND DISCOMFORTS: Risks involved with this study are related to possible side effects or allergic reaction caused by the study drug. These side effects may include nausea, strange dreams, fast heart rate, increased blood pressure, increased amount of saliva or death. These side effects have not been observed at the dose you will be given if you receive the study drug. Another risk is that you may not notice a decrease in the amount of pain you feel after surgery. We ask that you complete a questionnaire that describes your pain after surgery and that you mail this questionnaire back to us. You will be visited in your hospital room or called at home the day after surgery by one of the investigators. Additionally, filling out the questionnaire will require about 5-10 minutes of your time.

ALTERNATIVES TO PARTICIPATION: If you do not agree to or do not wish to participate in the study, your surgery will continue with the standard treatment of your pain that would be available to any patient if he/she were not in the study.

COMPENSATION: You will not be paid for your participation in this study.

CONFIDENTIALITY OF RECORDS: The case records from this study will be available for review by members of the Institutional Review Board at Madigan, Institutional Review Board at University of Texas at Houston, and by representatives of the Food and Drug Administration (FDA) and other governmental agencies as part of their normal duties. All records will be kept in a confidential form. Otherwise, only the individuals conducting this study will have access to the records from this study. Information gained from this study may be used as part of a scientific publication, but you will in no way be personally identified. Complete confidentiality cannot be promised, particularly for military personnel because information bearing on your health may be required to be reported to appropriate medical or Command authority.

NEW FINDINGS: Significant findings that occur during this study that might affect your decision to participate in this study will be discussed with you. Any significant findings developed from this study will be available to you and may be obtained from your physician.

REMOVAL STATEMENT: Your participation in this study may be terminated without your consent if conditions occur which might make your continued participation dangerous or detrimental to your health; or if military contingency requires it; or if you become ineligible for military care as authorized by Army regulation.

OTHER INFORMATION: If you should require medical care for injuries or disease which result from participation in this study, the medical care to which you will be entitled is the same as that which you are already entitled as a DoD health care beneficiary. This does not include domiciliary (home care) or nursing home care.

You are encouraged to ask any questions, at any time, that will help you to understand how this study will be performed and/or how it will affect you. You may contact CPT Dennis R. Turner at (253) 968-1506.

Also if you have any questions or concerns about this study or your rights as a study subject, you may contact the Institutional Review Board, Madigan Army Medical Center, Tacoma, WA, 98431, (253) 968-0149

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE AGREEING TO PARTICIPATE IN THIS STUDY. You will be given a copy of this consent document for your records.

I do o do not o (check one & initial) consent to the inclusion of this form in my outpatient medical treatment record.

SIGNATURE OF VOLUNTEER	DATE	SIGNATURE OF LEGAL GUARDIAN
PERMANENT ADDRESS OF VOLUNTEER	TYPED NAME OF WITNESS SIGNATURE OF WITNESS DATE SIGNED	

APPENDIX C

Standard Anesthetic Plan

1. Prior to administration of medication, verification of study enrollment will be done. This includes consent to participate, signed anesthesia/surgical consent, and review of study procedures.

2. Metoclopramide 10 mg IV and midazolam 1-2 mg IV will be given preoperatively. Upon arrival to the operating room, standard monitoring devices will be attached to the patient. The induction sequence will include fentanyl 3 mcg/kg and propofol 2 - 2.5 mg/kg with lidocaine 20 mg/100 mg . Immediately following induction, either ketamine .1 mg/kg or normal saline of equal volume will be administered followed by succinylcholine 1 mg/kg will be used.

3. Maintenance of anesthesia will include sevoflurane and oxygen/nitrous oxide, at 70% nitrous oxide, mixture titrated to maintain oxygen saturation (SpO2) > 95%. Blood pressure and heart rate will be maintained within 30% of baseline with appropriate medications.

4. Prior to emergence, dolasetron 12.5 mg IV will be administered to decrease the incidence of postoperative nausea and vomiting (PONV), and an orogastric tube will be inserted to empty the stomach of blood.

5. Extubation will be performed when throat packs have been removed, the subject is awake, and the necessary parameters for extubation criteria are met. Subjects will be transferred to the postanesthesia care unit (PACU) with supplemental oxygen.

6. Postoperative medication in the PACU will include morphine 2-4 mg IV every 5 minutes as needed to a maximum dose of .2 mg/kg, dolasetron 12.5 mg IV, and metoclopromide 10 mg IV for control of PONV if needed.

7. The ENT surgeons will use a standard pain management protocol developed by the ENT service to manage subjects' postoperative pain after discharge.

APPENDIX D

Teaching Instrument for the Numeric rating scale (NRS)

The NRS is and eleven-point pain assessment tool that evaluates (by numeric scoring) the intensity of pain, commonly used after surgery to assess initial levels of pain and then subsequent levels of pain following the administration of an analgesic.

To ensure consistency in teaching, each subject who has consented to participate in the study must be instructed how to use the NRS in the same manner. Please instruct patients to use the NRS as in the following example:

> Sir or Ma'am, we are studying the effectiveness of a pain medicine that will be given before surgical incision. While you are in this study you will be asked to rate your pain on a scale of zero to ten several times following surgery and then also asked to use it while at home.
>
> Zero will represent absolutely no pain and ten will represent the most pain you can possibly imagine. Please us this scale to describe your pain. Each time you are asked how your pain is, please respond with an actual number and then describe the pain further to your nurse.

APPENDIX E

Data Collection Tools

Preoperative/Intraoperative Information

Study Number: _____ UPPP Tonsillectomy Adenoidectomy T&A

Preoperative Information:

Age: _____Gender: Male Female Ethnicity: _____

Height: _____ (inches) Weight: _____ (kilograms)BMI: _____

ASA: I II

Preoperative Medications:

Medication: _____Dose: _____Route: ____ Time: _____

Medication: _____Dose: _____Route: ____ Time: _____

Medication: _____Dose: _____Route: ____ Time: _____

Intraoperative Information:

Time of induction: _____

Time of ketamine/placebo administration: _____

Time of incision: _____

Duration of surgery: _____ Time of extubation: _____

Anesthetic study protocol met: YES NO

Intraoperative analgesics: YES NO

Medication: _____ Total dose: ____ Medication: _____ Total dose: _____

Intraoperative local anesthetics: YES NO

Medication: _____Dose: _____ Time: _____

Intraoperative complications/occurrences:

Postoperative Information and Medication Pain Log

Study Number: _____

PACU Nurse, please use this form to record the pain score and analgesic/medication usage for this patient. If the patient is admitted to a ward from the PACU, please indicate which ward the admission was to. Upon completion, please place this form in the designated box at the desk. Thank you for your help and cooperation with conducting this study.

Time of arrival to PACU: _____

Pain score on arrival to PACU:

0 1 2 3 4 5 6 7 8 9 10

Pain score 1 hour after arrival to PACU:

0 1 2 3 4 5 6 7 8 9 10

Pain score 4 hours after arrival to PACU:

0 1 2 3 4 5 6 7 8 9 10

Medication administered:

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Time of discharge from PACU: _____ Disposition: Home Ward (____)

Medication and Pain Log
(Take Home)

Study Number: _____

Thank you for accepting the invitation to our study. We will be calling you the first day after surgery to see how the surgery went. Please track the pain medicine you use and your pain scores at the intervals listed below. Upon completion of the 24-hour time interval, please mail your survey back to us at your earliest convenience using the self addressed envelope provided.

As a reminder, use the same pain scoring you used while you were in the hospital: 0 for no pain, and 10 being the worst pain imaginable. Thanks again!

Please circle the number below for your pain score at each of the following time intervals:

Pain score 4 hours after surgery:

0 1 2 3 4 5 6 7 8 9 10

Pain score 12 hours after surgery:

0 1 2 3 4 5 6 7 8 9 10

Pain score 24 hours after surgery:

0 1 2 3 4 5 6 7 8 9 10

Please record the pain medication you use below:

Medication: _____Dose: _____Time: _____

Medication: _____Dose: _____Time: _____

Medication: _____Dose: _____Time: _____

Medication: _____Dose: _____Time: _____

Medication: _____Dose: _____Time: _____

Medication: _____Dose: _____Time: _____

In the event the self-addressed postage paid envelope is lost, please mail this survey to:

Fort Lewis, WA 98433-9988

Medication and Pain Log
(In Hospital)

Study Number: _____

Ward Nurse, please use this form to record the pain score and analgesic/medication usage for this patient. Please use the time of arrival to PACU (recorded as "Recovery at" in the lower right corner of the Anesthesia Record) for the after surgery time periods below. Upon completion, please place this form in the designated box at the desk. Thank you for your help and cooperation with conducting this study.

Time of admission to ward: _____ Ward admitted to: _____

Pain score 4 hours after surgery:

0 1 2 3 4 5 6 7 8 9 10

Pain score 12 hours after surgery:

0 1 2 3 4 5 6 7 8 9 10

Pain score 24 hours after surgery:

0 1 2 3 4 5 6 7 8 9 10

Please record the pain medication you use below:

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Medication: _____ Dose: _____ Route: ____ Time: _____

Time of discharge from ward: _____ Disposition: Home Ward (____)

Day of discharge from ward was (circle one) same / following day of admission to ward.

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VITAE

CPT Dennis R. Turner

Dennis Turner was born in Salt Lake City, Utah on 21 November 1965, the son of Roger Turner and Kathleen Turner. While a Junior at South High School, he enlisted in the US Army Reserve as a Private in the specialty of Combat Medical Specialist. After graduating from high school in 1983, Dennis went through the Army Basic Training at Fort Sill, Oklahoma followed by the Combat Medical Specialist Course at Fort Sam Houston, Texas. After training, Dennis served in an Army Reserve unit as a medic and worked as a civilian at a local grocery store until 1987. In January 1987, Dennis enrolled in a practical nursing program at Salt Lake Community College, and graduated in December of 1987 with a Certificate in Practical Nursing. Following graduation, Dennis' military specialty was changed to Patient Care Specialist. Dennis began working as a Licensed Practical Nurse (LPN) in January 1988 at Wasatch Villa Convalescent Center. In January 1989, Dennis moved to Henderson, Nevada, and began work as a LPN at St. Rose Dominican Hospital (SRDH) on the Medical/Surgical floor. In May of 1990, Dennis graduated from Clark County Community College with an Associate of Applied Science degree in Nursing. After graduation and licensure as a Registered Nurse (RN), Dennis transferred to the Intensive Care Unit at SRDH. In December 1990, Dennis was activated for active service for Operation Desert Shield and Operation Desert Storm and stationed with the 2nd Field Hospital in Bremmerhaven, Germany in the Emergency Room. Dennis served in Germany until March 1991. While in Germany, Dennis began service as a Sergeant, but he received a direct commission to the US Army Nurse Corps and was promoted to the rank of Second Lieutenant. Upon returning home, Dennis returned to work at SRDH in the Intensive Care Unit and Emergency Room. In May 1994, Dennis graduated from the University of Nevada, Las Vegas with a Bachelor of

Science in Nursing. That same month, Dennis became the Clinical Director of the Cardiopulmonary Rehabilitation Department and began working part time in the Cardiac Cath Lab. In December 1996, Dennis married his wife, Christy. Their first daughter, Danielle was born in February 1998, and their second daughter was born in December 2000. In 1999, Dennis left his position as Cardiopulmonary Rehabilitation Clinical Director to work full time in the Cardiac Cath Lab in order to focus on critical care experience in preparation of anesthesia school. Also during the 1994 to 2001 time period while working at SRDH, Dennis served as American Heart Association Regional Faculty, Training Center Coordinator, and Instructor for Basic Life Support and as an Advanced Cardiac Life Support Instructor. In February 2001, Dennis entered active duty as a Captain and, in June of the same year, entered the US Army Graduate Program in Anesthesia Nursing at Fort Sam Houston Texas, affiliated with the University of Texas, Houston Health Science Center. In September of 2002, a son was born to the Turner family. Dennis has completed Phase I of the Program and anticipates completing Phase II at Madigan Army Medical Center in December 2003, earning a Master of Science in Nursing.

CPT Robert N. Ladd

Robert Ladd was born in West Palm Beach, FL November 21, 1972 to Tom and Miki Ladd. After graduating from Palm Bay High School in Melbourne, FL, in 1991, he enrolled at Western Kentucky University in Bowling Green, KY on a 4-year ROTC scholarship. In 1995, Robert received a Bachelors of Science in Nursing with a minor in Military Science and a Distinguished Military Graduate (DMG). His first duty assignment as a commissioned officer was at Fort Stewart, GA in November of 1995. At Winn Army Community Hospital, CPT Ladd worked on the Med-Surgical ward and the Intensive Care Unit (ICU) for one year each. His next duty assignment was at Tripler Army Medical Center (TAMC), HI after completing the Army Critical Care Course at Brooke Army Medical Center. While assigned at TAMC, CPT Ladd worked in the Surgical and Medical ICUs. Also while in Hawaii, he was assigned to the 8th Forward Surgical Team (FST), 25th Infantry Division, Schofield Barracks as the critical care nurse. In 2001, he was accepted into the U.S. Army Graduate Program in Anesthesia Nursing. He has completed phase I of the program and is anticipating completion of phase II at MAMC to earn the degree of Master of Science in Nursing.

CPT Carrie L. Pike

Carrie Pike was born in San Augustine, Texas, August 22, 1975 and graduated from West Sabine High School in Pineland, Texas, 1993. She attended the University of Texas at Austin and received a BSN in December 1997. In January 1998, she began a six month preceptorship in the Neurological, Cardiac and Medical-surgical Intensive Care Units at Seton Medical Center in Austin, Texas. She was a staff nurse in all three units and functioned as team leader (or head nurse) when scheduled until February, 2001. She entered into the United States Army in February 2001 after her acceptance into the U.S. Army Graduate Program in Anesthesia Nursing. She has completed phase I of the program and is anticipating completion of phase II at MAMC to earn the degree of Master of Science in Nursing.

This thesis was typed by the investigators.