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13. ABSTRACT *(Maximum 200 words)*
Fifty to 75% of patients report that postoperative pain management is grossly inadequate. A contributing factor to this analgesic deficit may be hyperalgesia, a phenomenon whereby the intensity and duration of painful stimuli are enhanced. Activation of the N-methyl-D-aspartate (NMDA) receptor due to surgical insult has been shown to initiate and maintain central sensitization , the hyperexcitable state within the central nervous system the produces hyperalgesia. Ketamine, an NMDA receptor antagonist, administered preemptively may inhibit central sensitization and thereby reduce postoperative pain perception. Further, the efficacy of ketamine may be influenced by sex or gender differences that have not been clearly elucidated. In this 2 X 2 factorial, double blind, placebo-controlled study, 37 female and 18 male (N =55) ASA 1-3 participants who underwent elective laparoscopic surgery were randomly assigned to receive either a perioperative low dose ketamine infusion at 3.125 mcg/kg/min or a saline infusion at the same rate. Early pain perception was measured by time to first request (TTFR) for analgesic medication. Prolonged pain perception was derived from participants' 24-hour opioid consumption. The 100 millimeter visual analogue scale (VAS) measured pain perception at the following four time points, time to first request for an analgesic, 30 minutes after arrival in the postanesthesia care unit (PACU), at time of discharge from PACU, and 24 hours after termination of the perioperative infusion. No significant demographic differences among groups ($p > .05$) were found. Further, no significant differences were found among groups with regard to TTFR, 24-hour opioid equivalent usage or repeated measures pain perception, using the VAS. However, a significant difference in TTFR (p,.49) was found in females in the luteal phase of the menstrual cycle when compared to women in the follicular phase or nonmenstruating women and men. The findings in this study may reflect NMDA receptor antagonism or activiation of kappa-opioid receptor or both via ketamine administration.. With this new evidence suggesting a hormonal influence on the efficacy of ketamine, we recommended further investigation in this area.

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EFFECTS OF PERIOPERATIVE LOW DOSE KETAMINE INFUSION ON POSTOPERATIVE PAIN PERCEPTION IN MALES AND FEMALES UNDERGOING LAPAROSCOPIC SURGERY

By

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A Cluster Research Study

submitted in partial fulfillment

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ABSTRACT

Fifty to 75% of patients report that postoperative pain management is grossly inadequate. A contributing factor to this analgesic deficit may be hyperalgesia, a phenomenon whereby the intensity and duration of painful stimuli are enhanced. Activation of the N-methyl-D-aspartate (NMDA) receptor due to surgical insult has been shown to initiate and maintain central sensitization, the hyperexcitable state within the central nervous system the produces hyperalgesia. Ketamine, an NMDA receptor antagonist, administered preemptively may inhibit central sensitization and thereby reduce postoperative pain perception. Further, the efficacy of ketamine may be influenced by sex or gender differences that have not been clearly elucidated.

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No significant demographic differences among groups ($p > .05$) were found. Further, no significant differences were found among groups with regard to TTFR, 24-hour opioid equivalent usage or repeated measures pain perception, using the VAS. However, a significant difference in TTFR ($p < .049$) was found in females in the luteal phase of the menstrual cycle when compared to women in the follicular phase or nonmenstruating women and men.

The findings in this study may reflect NMDA receptor antagonism or activation of kappa-opioid receptors or both via ketamine administration. With this new evidence suggesting a hormonal influence on the efficacy of ketamine, we recommend further investigation in this area.

TABLE OF CONTENTS

EFFECTS OF PERIOPERATIVE LOW DOSE KETAMINE INFUSION ON

POSTOPERATIVE PAIN PERCEPTION IN MALES

AND FEMALES UNDERGOING

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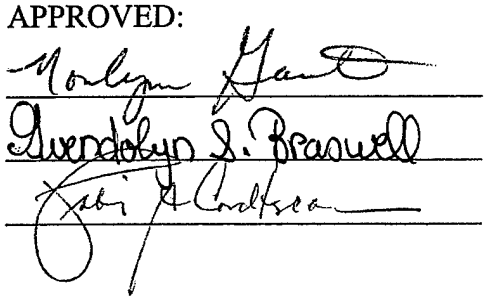

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NOTICE OF APPROVAL TO BEGIN RESEARCH October 18, 2002

HSC-SN-02-027– "Effects of Perioperative Low Dose Ketamine Infusion on Postoperative Pain Perception in Males and Females undergoing Laparoscopic Surgery"
P.I.: Warren Cusick, 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.

RATIFIED: At a Convened Meeting

APPROVAL DATE: October 18, 2002 EXPIRATION DATE: September 30, 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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LIST OF TABLES

LIST OF FIGURES

CHAPTER I

Introduction

Postoperative pain is detrimental to a recovering patient. Surgical injury and pain initiate the body's stress response manifested by metabolic, hormonal, and immunologic changes (Weissman, 1990). Postoperative patients experiencing pain have been found to have significant abnormalities of cellular immunity that can lead to delayed healing and recovery (Weissman). In a study by Page, Blakely, & Ben-Eliyahu (2001), research findings using the Fischer 344 rat suggest that the management of perioperative pain is a critical factor in preventing surgery-induced decreases in host resistance against metastasis. If similar relationships between pain and metastasis exist in people, then pain control must become a priority in the postoperative care of individuals with solid tumor cancer.

Surgery-induced postoperative pain may induce two changes to the nervous system: peripheral sensitization and central sensitization, with the latter being an increase in the excitability of spinal neurons (Woolf & Chong, 1993). Central sensitization is induced by activation of N-methyl-D-aspartate (NMDA) receptors in the dorsal horn of the spinal cord. Our goal is to study the efficacy of preventing central sensitization with the use of a perioperative low dose ketamine infusion. If the data revealed a treatment effect, then improvements in postoperative pain management could be realized and improve the surgical experience for patients.

Adequate postoperative pain management continues to be a challenge for the healthcare profession. Since a classic report by Marks and Sachar (1973), there continues to be a need for improving pain management. The authors Owen, McMillan, and Rogowski (1990), through a study of 250 elective surgery patients, found that 28% of postoperative patients had severe pain during the first 24 hours following their procedure. Filos & Lehmann, (1999) estimate that approximately 50% to 75% of patients have inadequate pain relief.

The cost of postoperative pain to the patient and the healthcare industry is considerable. Although clinical economics lacks the pure humanitarian focus that comprises the foundation of pain management, there are choices to be made that effect costs. The calculated cost of acute postoperative pain medication suggests that the cost as a function of hospital stay is influenced highly by the use of a few expensive medications (Dalton et al., 2000). The ideal scenario is to maximize pain control and minimize costs. The difficult part is discerning between cost-benefit since few data are available to guide practitioners (Dalton et al.).

Postoperative pain management is a complex problem and may be affected by variables such as education (staff and patient), culture, age, and even sex. Our study was designed such that differences in postoperative pain perception between males and females were observed. Unfortunately, a complete understanding of the relationship between sex and postoperative pain is nonexistent. However, there is evidence within the literature to suggest differences in pain perception between males and females. For example, Averbuch & Katzper, (2000) found that women experience greater analgesic efficacy than men following the administration of narcotic analgesics. Although our study did provide answers that will account for the difference in males and females, it did add to the limited body of knowledge concerning pain perception and sex differences.

The overall purpose of this study was to investigate the effects of a low dose perioperative infusion of propofol plus the noncompetitive NMDA antagonist, ketamine, compared to propofol alone in attenuating surgery-induced postoperative pain in laparoscopic surgery patients using (a) total 24 hour postoperative morphine equivalent consumption (Appendix G) (b) time to first request for postoperative supplementary analgesia and (c) worst pain score on a visual analogue scale as measures of postoperative pain relief. The secondary purpose was to examine gender differences in response to a low dose perioperative infusion of propofol plus ketamine compared to

propofol alone in attenuating surgery-induced postoperative pain in the same set of surgical patients.

Statement of the Problem

This research was derived from two questions: (1) is the combination of propofol plus ketamine delivered as a low dose perioperative infusion more efficacious than propofol alone on postoperative pain perception in laparoscopic surgery patients and (2) is a low dose perioperative infusion of propofol plus ketamine more efficacious in males compared to females?

Significance of the Problem

Findings from the proposed study were important for many reasons. Although alleviation of postoperative pain is primarily to provide patient comfort, it also serves to block adverse nociceptive induced responses to pain. These responses can lead to organ damage and include an increase of catabolic hormones, activation of cytokines, complements, arachidonic acid metabolites, nitric oxide, and free oxygen radicals (Kehlet, 1999). These changes lead to abnormalities of cellular immunity that can lead to delayed healing and recovery (Weissman, 1990). Importantly, research suggests that inadequate pain management in cancer patients leads to a decrease in host resistance against metastasis. According to the American Cancer Society (*Cancer Facts & Figures 2002*, 2002), approximately 555,500 people will die from cancer this year. This amounts to more than 1500 people per day. The cost to society is 156.7 billion dollars in direct and indirect costs. Postoperative pain's link to cancer is germane to both males and females as cancer is prevalent in both populations and is only second to heart disease as the leading cause of death.

Until 1993, women were largely excluded from clinical phase I and early phase II drug trials based on the possible risks of studying women with child-bearing potential (Beierle, Meibohm, & Derendorf, 1999). This institutionalized bias left a void in what could have been a more complete body of knowledge dealing with sex differences in pain

perception. This research assisted in filling this void by recruiting females and males without bias.

This study was limited in that its quasiexperimental nature did not describe how or why gender differences exist. However, the proposal and subsequent experimentation was built within a framework of sound theory that is well known and accepted by the field of anesthesia.

Theoretical Framework

Gate Control Theory

The Gate Control Theory is based on the work of Melzack and Wall (1965). The discussion of this theory will focus on A-β and C type afferent pain fibers, the structure and function of the proposed "gate" in the dorsal horn, and physiologic pain modulation mechanisms that descend from the brain or are constitutive in the dorsal horn. There is evidence (Woolf, 1983; Woolf & Thompson, 1991) pointing toward central sensitization, a state of hypersensitivity to noxious and non-noxious stimuli following a painful event such as surgery, which provides an important explanation of dorsal horn plasticity not completely described in the Gate Control Theory. Therefore, the Gate Control Theory was presented together with peripheral and central sensitization as the theoretical framework for this study (figure 1).

Within the framework of the Gate Control Theory, afferent impulses, such as those evoked from surgical tissue trauma, are transmitted to three functional spinal cord systems. Peripheral pain impulses enter the dorsal horn and synapse in the substantia gelatinosa, the first of the three spinal cord systems. The second system includes those fibers that ascend rhostrally to the brain in the dorsal columns. The third system involves central transmission cells that receive modified impulses from the substantia gelatinosa, where the gate control system is located (Melzack & Wall, 1965).

Melzack and Wall (1965) describe the substantia gelatinosa as a functional unit, which spans the spinal cord and consists of densely packed cells. These cells interrelate

by short fiber synapses and longer fibers from Lissauer's tract. The substantia gelatinosa is considered a gating site where small and large fiber afferent signals are modulated.

Gate Control Theory

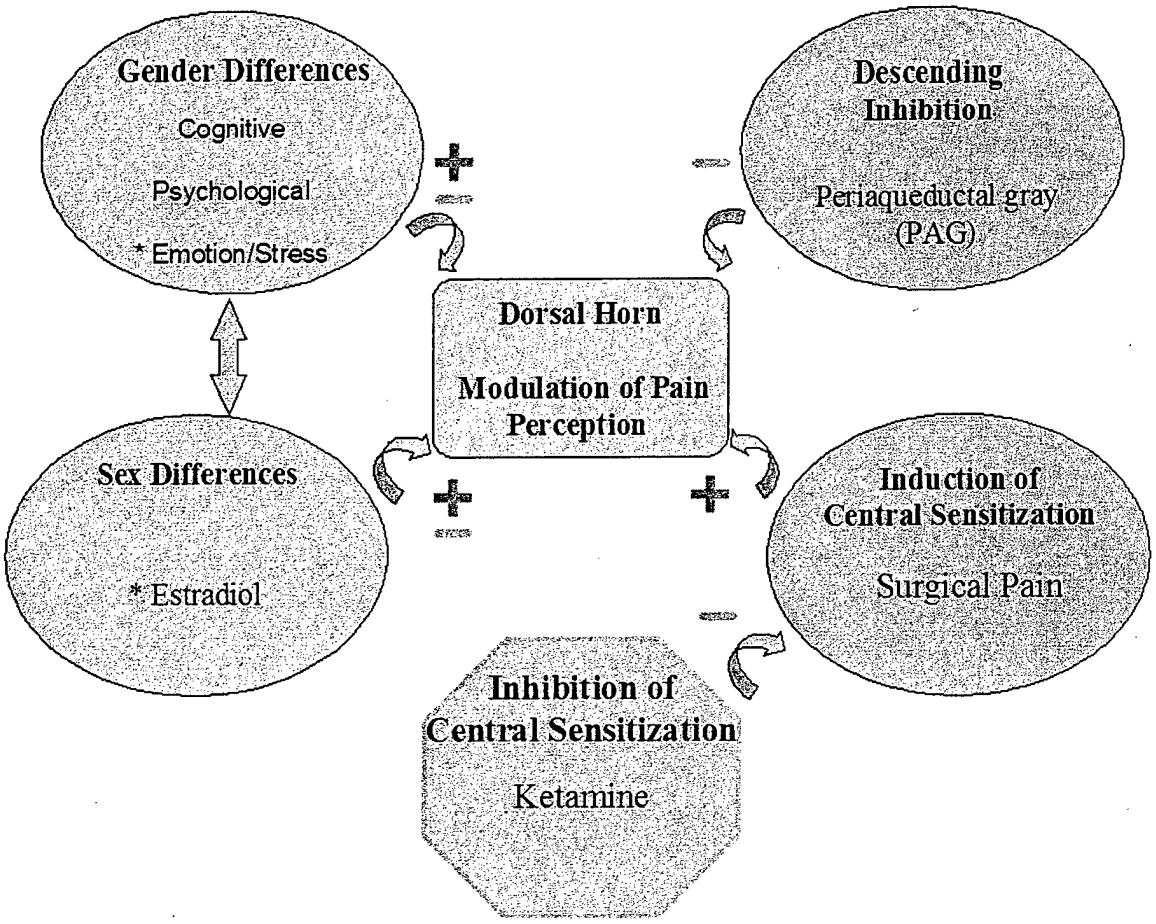

Figure 1. This framework marks the relationships between inducers (+) and inhibitors (-) of central sensitization, a state of increased responsiveness to benign and noxious stimuli, increased receptive fields, and decreased threshold. Surgical insult damages tissues releasing mediators that increase frequency and number of afferent fibers carrying pain signals to the dorsal horn cells initiating the changes of central sensitization. Dorsal horn cells summate arriving pain and descending inhibitory signals (PAG) including important modulating influences of sex (hormonal) and gender. Ketamine inhibits the induction of central sensitization.

Touch and pain signals from large and small afferent fibers, respectively, converge at the substantia gelatinosa in the spinal cord dorsal horn. Small afferent fiber impulses tend to activate the system and transmit information about painful stimuli rhostrally. Large fibers initially activate central transmission neurons that transmit pain; however, continued impulses arriving in large fibers tend to inhibit rhostral transmission of pain signals (Melzack & Wall, 1965). Afferent noxious and non-noxious signals alter the threshold of central transmission cells through a mechanism called summation.

The frequency of pain signals in large and small diameter afferents influences the overall output of the central transmission neurons. Activity in the large fibers inhibits transmission of pain signals (closes the gate), while activity in the small fibers facilitates pain transmission (opens the gate). The central transmission cells integrate arriving pain signals summating these both spatially and temporally. Spatial summation refers to the integration of the sheer numbers of arriving pain signals together with the frequency of arriving signals, or temporal summation (Woolf & Chong, 1993). Pain is experienced when the sum of spatial and temporal afferent pain signals exceed a given threshold established by modulating influences from the cortex and other central structures as well as large diameter afferents (Melzack & Wall, 1965).

Modulation not only involves neurons within the dorsal horn but also a complex supraspinally organized descending system. Melzack and Wall (1965) describe a subset of descending fibers that originate in centers where control of anxiety, emotion, prior experiences, and attention occur. Modulating contributions from the limbic system and somatosensory cortex descend to the gate in the dorsal horn and raise the threshold of central transmission cells (Melzack & Wall, 1965). A higher threshold raises the number of temporally and spatially summed stimuli required to send the pain signal centrally where pain perception occurs and, thus, the organism is afforded a level of modulation that reduces the noxious stimulus.

The modulation from higher centers exhibits sex differences. Estrogen receptors have a widespread distribution throughout the central nervous system with a sex-dependent dimorphic expression. Dimorphic receptors are also co-located with receptors responsible for pain and may explain why male and female subjects report different levels of pain following a nociceptive event. Menstrual cyclicity has been suggested to influence the pain experience and response. Given the hormonal changes associated with the menstrual cycle and concomitant affective fluctuation, nociceptive events may or may not be interpreted as painful (Berkley, 1997).

As the gate control theory suggests, ascending pain pathways can be modulated such that pain perception is decreased. The following sections describe neurochemical events associated with tissue damage including peripheral and central sensitization due to surgery, the ascending pain pathways, the role of the NMDA receptor in the afferent transmission of pain, evidence suggesting NMDA antagonism inhibits central sensitization, and finally physiologic and cognitive/psychosocial evidence that response to NMDA receptor antagonism may be gender/sex dependent. The following sections are described in detail to explicate the conceptual link between surgery-induced central sensitization, inhibition of central sensitization via NMDA receptor antagonism, and gender specific responses to NMDA receptor antagonism through the framework of the gate control theory.

Sensitization

Peripheral sensitization, a *post facto* consequence of tissue damage and chemical mediators released during an inflammatory response, alters transduction in nociceptors that normally have relatively high thresholds. Substance P and calcitonin gene related peptide (CGRP) are neuroactive substances that act on inflammatory cells, endothelial cells, and smooth muscle to produce vasodilatation and cellular leakage into the interstitial milieu surrounding A-β, Alpha-δ, and C fibers. Bradykinins, cytokines, histamine, hydrogen ions, leukotrienes, nerve growth factor, norepinephrine,

neuropeptides, potassium ions, prostaglandins, and serotonin (5-HT) are synergistically active at afferent terminals where these chemicals increase nociceptive transduction producing peripheral sensitization (Woolf & Chong, 1993). Peripheral sensitization is fundamentally different from central sensitization. It is characterized by the conversion of the Alpha-β fiber, a high threshold fiber that normally signals innocuous events, into a low threshold nociceptive transducer (Woolf, 1991; Woolf & Chong, 1993).

Central sensitization is characterized by three changes within the dorsal horn: 1) reduced threshold of dorsal horn neurons in the substantia gelatinosa, 2) increased responsiveness to both noxious and benign stimuli, and 3) subsequent expansion of the receptive fields. Receptive fields of dorsal horn neurons, described by Woolf & Chong (1993) are constituted by an area subdivided into two zones called the firing zone and the subliminal zone. The firing zone, generally the center of the receptive field, is the location of afferents that trigger action potentials in the dorsal horn neurons with an adequate stimulus. The subliminal zone circumferentially surrounds the firing zone and the afferent fibers originating here normally do not trigger an action potential in the dorsal horn. However, dorsal horn cells are in a prolonged depolarized state following the establishment of central sensitization and are easily brought to threshold by subliminal zone afferent fibers that normally carry subthreshold signals. Stubhaug (1997) describes an area of punctate mechanical hyperalgesia or tactile allodynia which surrounded the surgical wounds of the participants in his study. The area of hypersensitivity appears to include the firing and subliminal zones described by Woolf & Chong (1993) and was significantly larger in the placebo group suggesting the establishment of central sensitization, which will be discussed in detail next.

The initial step of sensitization in the dorsal horn includes Alpha-δ and C fibers generating slow synaptic potentials through release of glutamate, an amino acid transmitter, and two excitatory neuropeptides, substance P and neurokinin A. Glutamate acts on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors,

increasing the conductance of sodium through its ion channel. NMDA receptor ion channels are functionally blocked by magnesium. The magnesium block is reversed as sodium conductance through AMPA receptors depolarizes the cell. Calcium and sodium currents through NMDA receptors result in a long-lasting depolarization in the post-synaptic cell (Woolf, 1983; Woolf & Chong, 1993).

Calcium influx increases second messenger concentrations that activate protein kinase phosphorylation of membrane proteins, such as ion channels and the neurokinin-1 (NK-1) and neurokinin-2 (NK-2) receptors (Woolf & Chong, 1993). Prolonged excitatory post-synaptic potentials arriving from the expanded receptive field (following surgery) cause progressive depolarization. Subsequent afferent stimuli that previously would not have exceeded threshold trigger action potentials in the dorsal horn neurons which carries the pain signal rhostrally for interpretation. The NMDA receptor is largely responsible for the initial central sensitivity, maintenance of a reduced threshold, and hyperalgesia seen in acute pain states. Studies have demonstrated that administering an NMDA antagonist prevents the establishment of central sensitization (Coderre & Melzack, 1992; Stubhaug, 1997; Woolf & Chong, 1993).

NDMA Receptor

The NMDA receptor ion channel is blocked by magnesium and activation follows ligand binding and voltage-dependent reversal of the magnesium blockade. The voltage-dependent NMDA activation follows glutamate binding to the AMPA receptor causing its ion channel to open and sodium to enter the cell. The membrane potential reverses sufficiently to activate both voltage-gated calcium and NMDA receptor ion channels. The magnesium blocking the NMDA ion channel is removed, permitting the entry of calcium and sodium, with potassium efflux (Andersen et al., 1996; Coderre & Melzack, 1992; Woolf & Chong, 1993).

Following activation of the NMDA receptor, the intracellular concentration of calcium increases, activating second messenger systems. Persistent NMDA activation, as

in the post-surgical patient, leads to phosphorylation of membrane bound proteins and ion channels. Phosphorylation results in a membrane that has increasingly permeable with a persistent reduction in threshold. Central sensitization does not occur without the activation of the NMDA receptor (Wilder-Smith, 2000; Woolf & Thompson, 1991).

NMDA receptor antagonism has been demonstrated to prevent establishment of central sensitization from the increased afferent transmission secondary to surgical tissue damage. Research investigating the NMDA antagonist, ketamine, describe outcomes where opioids clearly failed to prevent central sensitization, suggesting that the NMDA receptor initiates and maintains central sensitization (Stubhaug, 1997; Woolf & Chong, 1993).

NMDA Antagonist - Ketamine

Orser, Pennefather, and MacDonald (1997) described two mechanisms of action whereby ketamine inhibits the NMDA receptor. First, ketamine blocks the open channel and reduces channel mean open time. Secondly, ketamine decreases the frequency of channel opening through an allosteric mechanism. The predominance of closed channel blockade was observed at low concentrations of ketamine. It was theorized that the analgesic properties of ketamine might be the result of closed rather than open channel blockade. Therefore, ketamine has clinical utility to oppose the action of glutamate on NMDA receptors and prevent depolarization to an easily triggered threshold or a central sensitization state (Sandler, Schmid, & Katz, 1998).

Sarton et al. (2001) demonstrated the efficacy of ketamine at μ-opioid receptors and NMDA receptors. Using 2 μ-opioid receptor knockout mice and a control group of their wild-type littermates, the investigators administered intraperitoneal S(+) ketamine in doses of 0, 10, 100, and 200-mg/kg. The mice were exposed to a tail-immersion and hotplate antinociceptive assays. Both groups of mice type demonstrated increased latencies in the hotplate test, with the longest latencies to tail flick observed in wild-type mice with intact 2 μ-opioid receptors. The knockout mice did not experience any

ketamine-induced antinociception with tails exposure to 54^0 C water. The authors suggested that ketamine administration, acting at supraspinal μ-opioid receptors, resulted in the observed supraspinal analgesia and respiratory depression.

Several conclusions may be drawn from the two studies presented in this section. First, ketamine has activity at more than one receptor type, which contributes to its efficacy in analgesia. Second, the distinction between the two antinociceptive tests conducted by Sarton et al. (2001) is important. The tail flick test is a spinal reflex, whereas the hotplate test is regarded as a supraspinal reflex. The investigators concluded that S(+) ketamine failed to demonstrate an effect in the 2 μ-opioid receptor knockout mice in the tail flick test, demonstrating the importance of the μ-opioid receptor in spinal antinociception while the same was not demonstrated for non-μ-opioid receptors. However, the non-μ-opioid receptor contributed 40% of the supraspinally-mediated antinociception. The studies discussed in this section suggest a dichotomy of activity where ketamine confers analgesia via the μ-opioid receptor and prevents central sensitization via the NMDA receptor. Activity at the μ-opioid and NMDA receptor are important determinants of perceived pain; however, sex differences contribute to the complex pain system and may suggest alternative approaches to analgesia in males and females.

Gender/Sex Differences in Pain Perception

Pain perception, according to the Gate Control Theory, is a function of processing in the thalamic reticular formation, the somatosensory cortex, and limbic system. During critical developmental periods, gonadotropic hormone levels influence the composition of the central nervous system resulting in sex-dependent differences. Hormone level fluctuation during the menstrual cycle and a near ubiquitous distribution of estrogen receptors throughout the central nervous system considered together with increased pain reports and decreased efficacy of opioid analgesics in females suggest different mechanisms of endogenous analgesia (Berkley, 1997; Melzack & Wall, 1965).

Casey (1999) demonstrated several gender differences related to pain tolerance and cerebral blood flow during painful stimulation. First, females ($n = 10$) rated the intensity of a 40 °C exposure of their non-dominant forearm the same as males ($n = 10$). When the temperature was increased to a noxious 50 °C, female and males described the exposure as painful; however, females rated the exposure as significantly more painful than the male participants, $p < .0052$. Second, PET analysis of males and females revealed overlapping activation patterns of the bilateral premotor cortex, and contralateral anterior cingulate cortex, cerebellar vermis, and posterior insula. Using a technique called direct image subtraction, the investigator uncovered significantly greater contralateral prefrontal cortex activation in females. Female participants also demonstrated a significantly greater activation, $p < .05$, in the contralateral insula and thalamus than males. These findings demonstrate that there are important physiological differences in the central nervous system between males and females which may explain differences observed in pain behaviors and analgesic efficacy.

Studies combining inventories (surveys) of pain appraisals and gender roles followed by a cold pressor task, such as submerging a hand or foot in ice water, have been able to partly describe the complexity of gender differences in the pain experience. Sanford, Kersh, Thorn, Rich, and Ward (2002) studied two mediators, primary pain appraisal and gender role, to determine if a relationship between sex and response to experimental pain exists. Consistent with earlier findings (Otto & Dougher, 1985), results showed men demonstrated longer tolerance times to the cold pressor task, $t(142) = 2.06$, $p = .02$, compared to women; however visual analogue scale (VAS) pain ranks were not significantly different between sexes at quit point. Sex, femininity (defined on a gender role inventory scale), and threat appraisal as a predictors of tolerance time reached significance in regression analysis. The investigators suggested that the two psychosocial factors examined in this study, threat appraisal and gender role are not reducible to one

construct, rather these factors independently affect the relationship between sex and pain tolerance and account for observed sex differences.

According to Beierle et al. (1999), gender differences in absorption and bioavailability are not common and do not appear to have clinical significance. Drug distribution is affected by vascular and tissue volume, or the ratio of lean body mass to adipose tissue mass. Generally, women weigh less and have a higher percentage of body fat than men. Menstrual cycle hormone level fluctuations impact water and electrolyte balance; however, these changes in volume of distribution have not shown to have implications in the clinical setting (Kashuba & Nafziger, 1998).

Sex differences in metabolism and elimination of drugs may have important clinical consequences. Estrogen may decrease oxidation activity of the cytochrome P450 system, whereas progesterone may either inhibit or induce oxidation. Females generally have a lower glomerular filtration rate (GFR), which may have an impact on the elimination of many drugs. However, weight could not be ruled out as the causative factor for variations seen in GFR (Beierle et al., 1999).

In 1993, the Food and Drug Administration published new drug study research guidelines with a new focus on gender differences. The guidelines emphasized three pharmacological issues with implications for future studies: (a) the pharmacokinetic effects of the menstrual cycle and menopause status, (b) the pharmacokinetic effects of estrogen and oral contraceptives, and (c) oral contraceptive influence on effectiveness of a therapeutic agent (Beierle et al., 1999). While there is evidence suggesting that sex and gender affect pain perception, the relationship between these variables is not completely clear and requires further inquiry.

Purpose

The overall purpose of this study was to explore the effects of a low dose perioperative infusion of propofol plus ketamine, a noncompetitive NMDA antagonist, compared to propofol alone in attenuating postoperative pain perception in laparoscopic

surgery patients. The secondary purpose was to examine gender differences in response to a low dose perioperative infusion of propofol plus ketamine compared to propofol alone in attenuating postoperative pain perception in this sample of surgical patients.

Definition of Terms

Postoperative Pain.

Conceptual definition: Pain experienced in the postoperative period related to surgical tissue trauma and concomitant algesic-producing disease processes.

Operational definition: Patient report of pain measured on a 100 mm visual analogue scale (VAS) marked and scored at four time points: (a) 30 minutes after arrival in the PACU, (b) at the time the participant first requested an analgesic, (c) at PACU discharge, and (d) at 24 hours, which was on the ward or recorded at home on a 100 mm VAS sent home with the patient with instructions and a stamped envelope. The time interval to first analgesic medication request and total milligrams of analgesic used in the PACU was an indicator of pain threshold and pain.

Postoperative Period.

Conceptual definition: The time immediately after surgery.

Operational definition: The first 24 hours following laparoscopic surgery.

Rescue Analgesia.

Conceptual definition: The medication administered for pain upon patient request postoperatively.

Operational definition: Rescue analgesia was the total amount of *pro re nata* (PRN) narcotic analgesic administered, measured in morphine equivalent doses, for breakthrough pain during the first 24 hour postoperative period.

Problem Statement

Did a perioperative infusion of low dose propofol plus ketamine inhibit postoperative pain as evidenced by a lower VAS, less 24 hour PRN narcotic analgesic requirement, and longer time to first request of PRN narcotic analgesic postoperatively

compared to a low dose propofol infusion alone in male and female laparoscopic surgery patients?

Hypotheses

1. During the postanesthesia recovery period, laparoscopic surgery patients who received a perioperative low dose infusion of ketamine should report lower pain scores, have requested less prn analgesic medication, and should have a longer time interval to first request for analgesic medication compared to the control group.

2. During the postanesthesia recovery period, female laparoscopic surgery patients should report higher pain scores, have requested more *pro re nata* analgesic medication, and the time interval to first request for an analgesic drug should be sooner compared to male patients.

Assumptions

1. Laparoscopic surgery was a painful procedure requiring an acceptable form of postoperative analgesia.

2. Patients' subjective pain scores were the most accurate determinant of postoperative pain. The time interval to first request for analgesic medication and the number of milligrams used were objective determinants of pain congruent with subjective reports of pain.

3. Males and females were different with respect to socialization, psychological, and physiological makeup and, therefore, perception and threshold for pain vary (Averbuch & Katzper, 2000).

4. Weight-based ketamine dosing should result in equal plasma levels between subjects.

5. Propofol should not impact postoperative pain scores.

Limitations

The researchers of this study realized four limitations that may have impacted generalizability of findings.

1. A convenience sample of laparoscopic surgery patients at one U.S. Army medical center participated in the study, which reduced generalizations to other surgical populations.

2. Hormone levels, serum proteins, electrolytes, and osmolarity were not measured, which limited drawing conclusions about gender differences based on these levels.

3. A subset of patients were discharged the day of surgery, which prevented some follow-up pain assessments.

4. Using a single, predetermined weight-based dose of ketamine instead of randomizing subjects to receive one of several doses of ketamine prevented the discovery of a dose-dependent gender differences.

Summary

The findings from this study may be important for several reasons. Current perioperative analgesic regimens often include opioids and other analgesics that fail to effectively prevent establishment of central sensitization. For millions of patients who undergo surgery annually, the administration of low doses of ketamine may reduce pain to levels unobtainable with opioids alone due to toxicities. The identification of activated NMDA receptors as an essential component in the establishment of central sensitization illuminates a role for ketamine, a non-competitive NMDA antagonist. Reduction in pain is important to reduce the negative physiological sequelae of poorly managed pain and can decrease post-anesthesia and same day surgery length of stay or prevent protracted inpatient stays. Sex differences were considered in this study as a growing body of evidence points to hormonal and gender-related influences on pain perception.

CHAPTER II

Review of Related Literature

This chapter is a review of studies, including animal and human evidence, for the important role of the NMDA receptor in the initiation and maintenance of central sensitization and hyperalgesia, evidence that NMDA receptor antagonists ameliorate central sensitization, and that the response to NMDA receptor antagonists may be gender/sex specific. The following topics will be addressed in detail: (a) the NMDA receptor as the initiator of central sensitization, (b) NMDA Receptor Antagonists with specific emphasis on the non-competitive antagonist, ketamine, (c) gender/sex differences in response to pain and NMDA receptor antagonists, (d) the pharmacology of NMDA receptor antagonists with specific emphasis on the non-competitive antagonist, ketamine, and (e) the relevance of this research to clinical practice. The studies reviewed in this chapter were obtained through the OVID and PUBMED search engines using the keywords: (a) central sensitization, (b) dorsal horn, (c) gender, (d) ketamine, (e) pain, and (f) peripheral sensitization. Additionally, we searched online full-text journals, both local and remote medical library holdings, and bibliographies from relevant studies and texts.

NMDA Receptors as the Initiator of Central Sensitization

Animal studies of experimentally induced chemical, inflammatory, mechanical, and neuropathic noxious stimuli have shown that the NMDA receptor is involved in inducing central sensitization. Noxious stimuli which is intense enough to produce tissue injury will generate prolonged post-stimulus sensory disturbances such as continuing pain, increased sensitivity to noxious stimuli, and pain following innoxious stimuli (Woolf, 1983). The following review of research highlights the role of the NMDA receptor in the induction of central sensitization.

An example of thermally induced hyperalgesia, using injury to the lateral edge of the foot of Wistar rat, was demonstrated in experiments by Woolf (1983). He developed an animal model where changes in the threshold and responsiveness of the flexor reflex

of a Wistar rat, following peripheral injury, were analogous to the sensory changes found in man. Electrophysiological analysis of the induced increase in excitability of the flexion reflex demonstrated that it arose from changes in the spinal cord as well as from peripheral changes. A thermal injury to the lateral edge of the foot was induced in the 28 animals. It was found that following a local response, such as inflammation to the site of injury; the rats' neurons exhibited an increase in spontaneous activity and a decrease in the threshold for an evoked response. Precisely which neuronal mechanisms were responsible eluded him at that time.

Meller, Dykstra, and Gebhart (1996) demonstrated that acute thermal hyperalgesia is produced by NMDA receptor activation and is mediated by activation of nitric oxide synthase and protein kinase C. The investigators placed intrathecal catheters in 75 male Sprague-Dawley. A noxious stimulus was provided by a 50 Watt projector lamp with a beam of heat radiated to the underside of the tail. Withdrawal latencies of the tail to noxious stimuli were determined using a tail flick (TF) device. Rats were either injected with NMDA or amino-3-hydroxy-5-methylisoxazole-4-proprionate (AMPA) and thermal withdrawal latencies were tested at 0.5, 1, 2, 5, and 10-minute intervals. Administration of NMDA produced a rapid dose-dependent thermal hyperalgesia, where the administration of AMPA failed to produce any evidence of thermal hyperalgesia.

Mao, Price, Hayes, Lu, and Mayer (1992) described hyperalgesia as one of the major clinical features of neuropathic pain syndromes that occur following peripheral nerve injury. The investigators sought to show the interaction between NMDA and non-NMDA receptor activation in post-injury hyperalgesia. The study used the adult male Sprague-Dawley rat. A painful peripheral neuropathy was produced by a procedure resulting in chronic constrictive injury (CCI). Pre-injury and post-injury experiments were conducted. Thermal hyperalgesia to radiant heat was assessed with a foot-withdrawal test. The intrathecal treatments with 1-hydroxy-3-aminopyrrolidone-2 (HA966) and 5-methyl-10,11-dihydro-5*H*-dibenzo(a,d)cyclohepten-5,10-iminemaleate

(MK-801), both non-competitive NMDA receptor antagonists, began 15 minutes before nerve ligation. To determine whether initiation of treatments with NMDA receptor antagonists reduced thermal hyperalgesia, six groups of CCI rats were used to test three doses of HA966 (5, 20, 80 nmol), two doses of MK-801 (5, 20 nmol), and one control group with saline. All groups were first tested before nerve ligation to obtain baseline foot-withdrawal and then tested on days 3, 5, 7, 10, and 15. Results showed that groups with the treatment of either HA966 or MK-801 had less hyperalgesia, $p < .01$. The authors demonstrate that treatment with a non-competitive NMDA receptor antagonist reduces thermal hyperalgesia.

An experiment by Ghorpade and Advokat (1994) sought to examine whether the excitatory amino acids (EAA's), acting through the NMDA receptor, might be involved in behavioral hyperalgesia produced by central injury. A total of 116 albino Sprague-Dawley rats were used as subjects. All rats were given an intrathecal catheter where as the experimental groups received a spinal transection to produce hyperalgesia. The tail flick (TF) was used for nociceptive assessment. A noxious stimulus was provided by high-intensity light on the tail. The experiment sought to show that ketamine anesthesia would prevent the development of TF facilitation after spinalization and enhance the antinociceptive effects of postoperative morphine and that ketamine would have an antinociceptive effect in spinal but not intact rats. The study showed that both systemic and intrathecal ketamine had an antinociceptive effect in spinally transected animals. The authors attributed this to the nature of ketamine in being "use dependent" where it exerts its effects primarily after the channel has been opened through prior nociceptive stimulation.

Woolf and Thompson (1991), using a mechanical stimulus, studied the question of whether windup is a possible trigger for the production of central hypersensitivity. The nerve to the posterior biceps femoris/semitendinosus muscle of adult Sprague-Dawley rats was exposed on one side. A standard mechanical stimulus was applied to each foot

every five minutes and the total number of spikes elicited was counted. Mustard oil was applied to a patch of skin on the dorsum of the foot. In the absence of treatment, the mechanical stimulus produced a stable response as defined by the total number of action potentials generated. Pretreatment with MK-801 at doses of 0.5 and 1.0-mg/kg provided a depression of the reflex. The significance of this study is the implied prevention of central sensitization through use of preemptive analgesia and continued support that central sensitization is mediated through activation of NMDA receptors in the dorsal horn.

A study by Haley, Sullivan, and Dickenson (1990) induced hyperalgesia with the use of subcutaneous injections of formalin. Their sample involved 35 Sprague-Dawley rats to show evidence for NMDA receptor involvement during prolonged chemical nociception in the rat. A subcutaneous injection of 50 μl of 5% formalin into the hind paw was used to induce prolonged noxious stimuli. Formalin has been shown to be a reliable model of prolonged noxious stimulation. The response to formalin occurs in two phases. The first phasic peak lasts for 10 min and then subsides into a silent period. The second tonic phase lasts for 60 min after administration and contains waves of burst activity in the neurons. The results demonstrated an absolute block of both peaks of the formalin response when the specimen received γ-D-glutamylglycine (DGG) intrathecally following the formalin. Conversely, the ability of an excitatory amino acid (EAA) receptor antagonist to affect the formalin response was decreased if not given as a pretreatment. The investigators deduced that the rapid reduction by DGG of the acute evoked C-fiber response of dorsal horn neurons implied EAA involvement in the transmission of acute inputs. The action of the NMDA antagonist 5-amino-phosphonovaleric acid (AP5) had a greater effect on the second acute phase compared to the first acute phase, which suggested that C-fiber stimuli produced by peripheral formalin caused a centrally amplified response involving activation of NMDA receptors.

Ma and Woolf (1995) designed a study to examine whether a non-competitive NMDA receptor antagonist, MK-801, could prevent the induction of mechanical allodynia following the activation of C-fiber afferents of different origins. A noxious stimulus was induced with electrical stimulation to the sural nerve of Sprague-Dawley rats at C-fiber strength and topical applications of irritant mustard oil were used to prolong the period of decreased threshold. Pretreatment with MK-801 completely prevented the sural conditioning stimulus from producing a threshold decrease, $p < .0001$. Pretreatment also decreased mustard oil induced enhancement of touch-evoked responses, $p < .0001$.

Taken together, these studies show that central sensitization induced by models of thermal, chemical, mechanical, or electrical neuropathic hyperalgesia are initiated and maintained by the NMDA receptor. The implication for pain therapy suggests blocking the NMDA receptor, the receptor responsible for the induction of central sensitization. Blocking the NMDA receptor can be achieved with the use of NMDA receptor antagonists.

NMDA Receptor Antagonists

Collingridge & Watkins (1994) describe the NMDA receptor as a glutamate-activated cation channel distinctly different from the non-NMDA class of ionotropic glutamate receptor. The NMDA receptor includes properties like a large single channel conductance, a high Ca^{2+} /Na^{+} permeability ratio, a voltage-dependent Mg^{2+} block, high affinity for glutamate, a requirement for glycine as coagonist, and relatively slow activation and deactivation kinetics. Together, these properties bring about the specific roles that NMDA receptors serve in the phenomenon named excitotoxicity. Research demonstrates that the use of NMDA antagonists block the NMDA receptor and prevent central sensitization.

Animal Studies

Animal models suggest that both competitive and non-competitive NMDA receptor antagonists are effective in inhibiting both central sensitization (Ghorpade & Advokat, 1994; Haley et al., 1990; Ma & Woolf, 1995; Mao, Price, Hayes et al., 1992; Meller et al., 1996; Woolf, 1983) and morphine tolerance (Andersen et al., 1996; Bharagava & Zhao, 1996; Bhargava & Thorat, 1997; Elliott, Minami, Kolesnikov, Pasternak, & Inturrisi, 1994).

The efficacy of intrathecal MK-801 to reduce nociceptive behaviors in rats with experimental mononeuropathy was explored by Mao, Price, Mayer, Lu, and Hayes (1992). Neuropathic pain was induced in Sprague-Dawley rats by dissecting the sciatic nerve, which resulted in constriction without compromising blood flow. Analgesia was measured using the foot-withdrawal test. Results showed that MK-801 pretreatment reduced thermal hyperalgesia, produced by radiant heat, following sciatic nerve ligation. The results suggest that NMDA receptor activation is needed for the induction of neuropathic pain following constrictive nerve injury.

Bhargava and Thorat (1997) studied the effects of a competitive NMDA receptor antagonist on κ-opioid receptors using the drug LY235959. The study consisted of male Swiss-Webster mice and male Sprague-Dawley rats. Analgesic effect was measured using a TF test. TF latencies to thermal stimulation were measured before and up to 240 min after the injection of LY235959. LY235959 was injected subcutaneously 10 min before injection of U-50,488H (κ-opioid agonist). In the mouse, results showed that the administration of LY235959 by itself did not modify TF reaction time. Mice that had induced tolerance to U-50,488H, were given an injection of LY235959 prior to each injection of κ-opioid agonist. These mice showed an attenuation of tolerance as evidenced by progressively higher values of analgesic response to U-50,488H. In the rat, the effect of LY235959 alone demonstrated an increase in the TF latency when compared to the controls. The pretreatment of rats with LY235959 was shown to increase the

induced analgesic effect. In both animals, the development of tolerance to the analgesic action of U-50,488H was blocked by LY235959, which suggests the role of NMDA receptor in the induction of central sensitization.

A study looking at the effects of competitive and noncompetitive antagonists of the NMDA receptor on the analgesic action of δ_1- and δ_2-opioid receptor agonist in mice was performed by Bhargava and Zhao (1996). Ten male Swiss-Webster mice were used for each treatment group. Analgesic response was measured by the TF test. MK-801 and LY235959 were used as non-competitive and competitive NMDA receptor antagonists respectively. Results showed that both competitive and noncompetitive antagonists dose-dependently antagonize the analgesia produced by δ_1- and δ_2-opioid receptor agonist. The mechanisms of the findings were admittedly unclear to the investigators.

The effect of NMDA receptor antagonists, LY274614 and MK-801, on analgesic tolerance to mu-opioid receptor agonists was conducted by Elliott, Minami, Kolesnikov, Pasternak, & Inturrisi (1994). The animal model was the adult CD-1 mouse. Analgesic response was measured using a standard TF apparatus. Tolerance to the opioid agonist morphine was produced over a 5 day period by injection. The pretreatment with MK-801 or LY274614 led to attenuation of mu-opioid analgesic tolerance. The experimenters surmised that the mechanisms of attenuation of morphine tolerance in this model are mediated through the same central nervous system pathway.

Animal models suggest that both competitive and non-competitive NMDA receptor antagonists are effective in inhibiting both central sensitization and morphine tolerance with some exception. However, human studies are limited in scope when compared to the research involving the animal model. Drugs available for human use which can provide NMDA receptor antagonism are limited to ketamine and dextromethorphan.

Human Studies

Human studies concerning NMDA receptor antagonism involve drugs that are approved for human use. Since ketamine will be reviewed as a dedicated topic, the following discussion will be limited to dextromethorphan.

Researchers Wu et al. (2000) investigated the use of preincisional dextromethorphan (DM) treatment for postoperative pain management after upper abdominal surgery. The sample consisted of sixty patients of either sex undergoing abdominal surgery. The researchers randomly assigned participants into one of four groups. The four groups were DM-10, DM-20, DM-40, and a control where each experimental group was premedicated with DM 10-mg, 20-mg, and 40-mg respectively. Analgesia was measured by the time to first trigger of patient controlled analgesia (PCA) morphine, PCA consumption and frequency, as well as the VAS. The results demonstrated that the groups receiving higher doses of DM showed better pain relief over a 3 day observation period, $p < .05$. PCA triggering frequencies were higher in patients receiving less DM while total morphine consumption was lower in the DM pretreated groups, $p < .05$. The experiment suggested that DM premedication provides a dose-dependent relief of postoperative pain, increased time to first PCA trigger, lower morphine consumption, and lower VAS as compared to a control group.

Another human study using DM was conducted by Kauppila, Gronroos, and Pertovaara (1995). The investigators attempted to attenuate experimental pain in humans with the use of DM. The sample comprised eight healthy adults (three women and five men), aged 22-54 years. Heat pain was measured using a feedback controlled contact thermostimulator. A thermal stimulus of 5 second duration was administered at four temperatures in random order. Heat pain threshold was quantitatively defined as the temperature at which participants reported pain to 50% of the stimuli. The threshold for mechanical pain was quantified using the Basile Analgesymeter. This device applied a linearly increasing pressure to the palmar skin of the fingertip. Ischemic pain was induced

using a tourniquet placed proximal to the cubital fossa and inflated to 200 mmHg. Patients were required to perform exercise with the ischemic hand and rate the intensity and unpleasantness induced by the ischemia. C-fiber activation was induced by topical application of capsaicin to a 4-cm^2 area of the skin at the forearm. DM was mixed with bitter lemon and sugar to mask the taste of DM. The effect of 100-mg of DM was tested in a double-blind, placebo controlled, crossover design. DM or the placebo was tested on a separate day with a one week interval between tests. Results failed to show a significant difference between experimental drug and the placebo. The results of this study contradict animal studies with DM that have demonstrated efficacy with intrathecal DM to alleviate hyperalgesia. Although the study does not support the hypothesis that the use of oral DM can attenuate pain at doses that are clinically applicable, problems inherent to the study may explain this contradiction. The sample size limited the power of the study to detect a difference. Even with a large effect size, a sample of eight is in question. The researchers were limited in the maximum dose related to adverse side effects associated with a 200-mg oral dose.

Studying the effects of NMDA receptor antagonists in humans are inherently limited when compared to equivalent studies in the animal model, specifically the rodent. The limitations are a function of FDA regulations concerning the allowable drugs for human use. The two drugs commonly used with the human model for clinical practice and experimental study are DM and ketamine. Improvements in the specificity of drugs like ketamine may lead to greater success in blocking central sensitization.

Ketamine

An *in vitro* study by Orser et al. (1997) using a patch clamp technique to study NMDA activated currents from cultured mouse hippocampal neurons found that ketamine inhibited the NMDA receptor by two different mechanisms: (1) Ketamine blocks the open channel, and (2) ketamine lowers the frequency of channel opening allosterically. In the cell-attached patches, ketamine caused a concentration-dependent

decrease in both the duration and the frequency of NMDA channel opening. In addition, externally applied ketamine caused an 89% decrease in the frequency of channel opening without a significant change in channel-open time. This supports the suggestion that ketamine works by at least two mechanisms. The investigators admit that it is not known what sites mediate open or closed blockade.

As mentioned earlier, Sarton et al. (2001) demonstrated the efficacy of ketamine at μ-opioid receptors and NMDA receptors. Using 2 μ-opioid receptor knockout mice and a control group of their wild-type littermates, the investigators administered intraperitoneal S(+) ketamine in doses of 0, 10, 100, and 200-mg/kg. The mice were exposed to a tail-immersion and hotplate antinociceptive assays. Both groups of mice type demonstrated increased latencies in the hotplate test, with the longest latencies to tail flick observed in wild-type mice with intact 2 μ-opioid receptors. The knockout mice did not experience any ketamine-induced antinociception with tails exposure to 54^0 C water. The authors suggested that ketamine administration, acting at supraspinal μ-opioid receptors, resulted in the observed supraspinal analgesia and respiratory depression.

Fu, Miguel, and Scharf (1997) studied the effect of preemptive ketamine on postoperative narcotic requirements. The sample consisted of a preemptive group (n=20) who were given 0.5-mg/kg ketamine followed by a ketamine infusion of 10-mcg/kg, which was discontinued at wound closure. Patients in the postwound closure (n=20) group were given 0.5-mg/kg of ketamine immediately following abdominal closure. Both groups received IV morphine in the PACU and were started on morphine PCA after discharge from the PACU. Postoperative pain was evaluated by measuring morphine consumption and VAS pain scores at rest. The results revealed that preemptive ketamine was more effective than postwound closure administration of ketamine as evidenced by a 40% reduction in postoperative morphine consumption. The potential variance in severity of surgical stress is a potential weakness of the study. The only measure of severity was length of procedure for which there was no intergroup difference.

The adjunctive use of low-dose ketamine in addition to general anesthesia was investigated by Roytblat et al. (1993). The study consisted of 22 women, ASA category I and II, undergoing open cholecystectomy. Patients older than 70 years of age, with severe respiratory disease, or currently receiving opioids were excluded. Patients were randomly assigned to receive ketamine IV (0.15-mg/kg 5 min prior to incision) or saline. Postoperative pain control consisted of a 2-mg bolus of morphine if their VAS was four or more. Patients when sufficiently awake were given morphine PCA with a 1-mg/hr basal rate, a 2-mg bolus, and a 10 minute lockout. This was continued for 24 hr without the use of other analgesics. Pain intensity, respiratory rate, heart rate and arterial blood pressures were recorded 1, 2, 3, 4, 5, 6, 12, and 24 hr postoperatively. The mean arterial blood pressure and heart rate were significantly lower ($p < .05$) in the ketamine group at 10 min and 20 min respectively, following induction of anesthesia. Time to first request for analgesia (10 ± 7 min in the control and 35 ± 5 min in the ketamine group) was shown to be significantly different between the groups. The clinical significance of this finding is that the ketamine group required less morphine for postoperative pain in the first 24 hr period. The control group required 60% more (mean 48.7 ± 1.25-mg) PCA morphine than those in the ketamine group (mean 29.5 ± 5.2-mg). Optimized postoperative analgesia with limited opioid use prevents sedation and respiratory depression. These findings support the implementation of preemptive analgesia with ketamine to prevent the induction of central sensitization.

The effect of ketamine on central temporal summation in humans was studied by Arendt-Nielsen et al. (1995). Twelve paid volunteers participated in two sessions separated by one week. Participants received ketamine and or placebo (saline) in a randomized, double-blinded, cross-over design. A ketamine loading dose of 0.5-mg/kg was given IV over 3 minutes. Following the bolus, an infusion of 9-mcg/kg/min was initiated. Pressure pain detection and tolerance thresholds were measured using a pressure algometer. Electrical stimulation was provided by computer-controlled stimulation to the

sural nerve. A single stimulus was defined as a 200 Hertz (Hz) pulse over 25 ms where a repeated stimulus was repetition of a single stimulus five times at 2 Hz (lasting 2 s). A baseline VAS was recorded and a VAS measurement was taken after each stimulation. The results showed ($p < .05$) that ketamine inhibited strong single electrical stimulus, mechanical stimulus, and repeated electrical stimuli. The authors deduced that the effect of ketamine on the repeated stimuli may be explained by ketamine's inhibition of central temporal summation. The authors conceded that complete agreement concerning the effect of ketamine and the site of action is lacking among authorities on the subject. The primary analgesic activity of ketamine may be secondary to its activity at the mu receptor (Elliott et al., 1994; Sarton et al., 2001)

The evidence suggesting the efficacy of ketamine on stimulation of primary and secondary hyperalgesic areas induced by capsaicin was presented in a human experimental study performed by Andersen et al. (1996). This goal of the study was to measure the effect of ketamine on the development of secondary hyperalgesia and the summation of activity in nociceptive and non-nociceptive afferents. The subjects were seventeen healthy male volunteers ranging in age from 21-29 years. After induction of hyperalgesia with the topical application of capsaicin to the dorsum of the foot, either ketamine (0.2-mg/kg loading dose) or placebo was infused. The loading dose was followed with an infusion rate equal to 5-mcg/kg/min. The results revealed that ketamine provided inhibition to induction of continuous, low intensity electrical stimulation in the secondary hyperalgesic area. The investigators stated that while ketamine failed to alter the pain intensity of a single electrical stimulus applied to the secondary hyperalgesic area, it did reduce the pain intensity when this same stimulus was applied to the primary hyperalgesic area. They then hypothesized that these findings suggest that NMDA receptor linked systems are involved in secondary hyperalgesia, summation, and central sensitization.

A related study by Stubhaug, Breivik, Eide, Kreunen, and Foss (1997) sought to evaluate a more specific measure of central sensitization by measuring the area of punctuate mechanical hyperalgesia surrounding the surgical wound. The research question asked if the induction and maintenance of central sensitization could be prevented by a low-dose infusion of ketamine given as a supplement to balanced anesthesia. The study consisted of two groups of 10 patients who were all living kidney donors. Before the start of surgery, 10 randomly assigned patients received an IV bolus of racemic ketamine followed by a continuous IV infusion of ketamine at 2-mcg/kg/min for 24 hours. The control group received placebo bolus and infusion. PCA morphine was used for postoperative analgesia. Punctuate mechanical hyperalgesia and temporal summation was measured using von Frey filaments. The results showed that the area of punctuate mechanical hyperalgesia was reduced significantly in the ketamine group 1, 3, and 7 days following the operation, $p < .01$ to $p < .001$. The results demonstrated that low-dose ketamine reduced the area of hyperalgesia and that blockade of NMDA receptors prevent central sensitization caused by nociceptive input during surgery.

The efficacy of ketamine, a competitive NMDA receptor antagonist, in preventing central sensitization is supported within the literature. The potential benefit to patients in reduced postoperative pain and a decrease in opioid use are quite clear. What are less clear are the differences between sexes in postoperative pain perception.

Gender and Sex

Animal Studies

The search for sex differences in rodents has been pursued avidly, the results of which are perhaps closer than human studies in describing the physiologic mechanisms of antinociception. Rodent studies using some form of stressor have successfully induced the endogenous antinociceptive mechanisms and generated evidence for the role of sex hormone influence in pain regulation.

Mogil, Sternberg, Kest, Marek, and Liebeskind (1993) conducted a swim stress induced analgesia (SSIA) experiment in a rodent model to determine sex differences using naloxone and dizoclipine to unmask any dimorphism in opioid and non-opioid antinociceptive components, respectively. The investigators demonstrated a dizoclipine (NMDA antagonist) reversal of non-opioid SSIA in both intact male mice and in ovariectomized female mice. Estrogen replacement in ovariectomized female mice re-established non-opioid SSIA dizoclipine insensitivity. Daily estrogen treatment given to castrated male mice did not prevent dizoclipine reversal of non-opioid SSIA. The investigators concluded that an estrogen-dependent SSIA is evident in female mice alone and this system is activated given a similar stressor that activates the non-opioid or NMDA system seen in male mice. The lack of response to estrogen by castrated male mice supports an explanation that the estrogen-dependent analgesic system in females may develop during ontogeny in the presence of estrogen.

In the next logical step, Sternberg et al. (1995) investigated whether hormone manipulation during development affects the organization of the non-opioid stress induced analgesic system to include the NMDA receptor that influences this system. Female mice pups were injected with either 100-mcg of testosterone or 0.025 ml sesame oil shortly after birth. Later, during post-natal week eleven, these mice were injected daily with either estrogen benzoate or sesame oil. In post-natal week twelve, the rodents were subjected to a 3 min swim in 15 °C water followed by injection with either the NMDA antagonist dizoclipine (MK-801) or saline, then 20 min post-injection the mice were exposed to a hot-plate maintained at 56 +/- 0.2 °C.

Estrogen-treated female mice displayed a greater level of analgesia, $F(1, 102) = 7.57$, $p < .05$, compared to female mice which received sesame oil. This greater level of analgesia was observed despite hormone treatment during neonatal life or the treatment with MK-801 or saline after the swim stressor. Female mice exposed to testosterone during neonatal life demonstrated significant non-opioid SSIA reversal following

MK-801 administration, $F(1, 53) = 4.31$, $p < .05$. Female mice treated with sesame oil shortly after birth did not have any significant reversal of the non-opioid SSIA when given MK-801 or saline. A significantly greater SSIA was displayed by female mice treated with testosterone during the neonatal period, $F(1, 53) = 6.382$, $p < .05$. This evidence demonstrates that the hormonal milieu present in early ontogeny or neonatal period, particularly the absence of testosterone in female rodents, partly determines the neurochemical organization of the sex-specific endogenous non-opioid SSIA system and the efficacy of that system (Sternberg et al., 1995).

Kavaliers, Colwell, and Choleris (1998) conducted a stress induced analgesia (SIA) study using biting fly exposure to induce the endogenous opioid and non-opioid SIA systems in deer mice. Sex differences were similar to previous results (Mogil et al., 1993), with male deer mice demonstrating a greater magnitude of analgesia through a naloxone-reversible endogenous opioid analgesia system. Additional findings of the non-opioid analgesic system mechanisms found similarity between male and female deer mice; however, sex differences influenced its effect. Male, but not female deer mice experienced an antagonism of non-opioid analgesia with the NMDA receptor antagonist, NPC 12626 (Kavaliers et al., 1998).

There is evidence pointing to estrogen-influenced biologic processes that increases endogenous enkephalin synthesis (Amandusson, Hallbeck, Hallbeck, Hermanson, & Blomqvist, 1999). In estrogen-injected Sprague-Dawley rats, an assay quantified a 24 to 183% increase in enkephalin messenger ribonucleic acid at four hours post-injection in the outer layer of the dorsal horn. This location includes the substantia nigra where nociceptive relay cells are concentrated, receiving inputs from descending inhibitory pathways and afferent nociceptive and non-nociceptive fibers. The quantification of increasing levels of enkephalin mRNA following injection of estrogen juxtaposed with normal menstrual cycle estrogen fluctuation provides an explanation of

sex-dependent mechanisms of pain modulation and differences observed between female rats and between female rats compared to male rats (Amandusson et al., 1999).

Animal studies provide evidence that a sex-dependent dimorphic stress induced analgesia system exists and that males, but not female mice experience a reversal of the non-opioid system when administered the NMDA antagonists, dizoclipine (MK-801) or NPC 12626. Hormone milieu was shown to be important, particularly the evidence presented by Sternberg et al. (1995) demonstrating that estrogen administration resulted in greater analgesia in female mice. This improved analgesia in female mice was still appreciated after the testosterone-induced non-opioid analgesic system was antagonized with a NMDA antagonist. More importantly, the rodent studies discussed in this section (Kavaliers et al., 1998; Mogil et al., 1993; Sternberg et al., 1995) have demonstrated the existence of sexually dimorphic stress induced analgesia systems, which may help explain sex differences observed in human pain studies. Evidence that the NMDA receptor plays a larger role in the stress induced non-opioid analgesia system in male mice may also help explain sex differences observed in humans.

Human Studies

In this section, studies that distinguish sex on the basis genetic sex-trait characteristics and hormonal influences will be used to discuss "sex differences". Gender differences will be discussed when some basis in the study describes role differences, cultural expectations, experiences, and other variables which influence masculinity and femininity and pain behaviors associated with those qualities.

In order to understand the results of experiments investigating sex differences in the context of hormonal fluctuations during the menstrual cycle, a short description of the menstrual cycle is in order. There are three divisions in the menstrual cycle: (a) the follicular phase, including menses, (b) ovulation, and (c) the luteal phase. The follicular phase begins the menstrual cycle with menses on day one. Menses continues for about five days during which time estrogen and progesterone levels are relatively low with an

episodic, pulsatile pattern of follicle stimulation hormone (FSH) and Luteinising hormone (LH) release from the adenohypophysis. The late follicular phase is characterized by a rapid increase in estrogen concentration over the final two to three days of the phase, estrogen-dependent surges of FSH and LH which lead to an increasing progesterone level, ending with ovulation near the peak of estrogen levels. The early luteal phase hormone variation is characterized by a brisk decline in estrogen levels and increasing progesterone levels. In the mid-luteal phase, the progesterone level reaches a plateau and estrogen levels rise and reach a second peak on or about days 20 to 22 followed by a decline back to the relatively low levels described on day one of the menstrual cycle (Kashuba & Nafziger, 1998).

Hellstrom and Lundberg (2000) conducted a repeated measures study to determine if pain threshold or pain tolerance is influenced by gender or phase in the menstrual cycle. Twenty-two female and 19 male participants underwent a cold pressor test once during days 2 through 4 (follicular phase) and once during days 20 through 24 (luteal phase) corresponding to the female participants' menstrual cycle. There were no significant differences between males and females in pain threshold. An increased pain threshold was reported as a significant effect, $\underline{t}\ (21) = -1.80$, $p < .05$, in female participants in days 20 through 24 (luteal phase) of their menstrual cycle, when estrogen levels are increased, compared to females in days 2 through 4 (follicular phase) when estrogen levels are relatively low. There were no significant differences in pain threshold between female participants during days 5 through 19 of their menstrual cycles. This evidence points to a sex-dependent difference in pain modulation that varies with estrogen levels. The investigators suggest that pain threshold is predominantly influenced by biological processes or sex differences, whereas pain tolerance was related to psychological factors associated with gender differences (Hellstrom & Lundberg, 2000).

In a study comparing sex differences in analgesia between males and females following a third molar extraction, Gear, Miaskowski et al. (1996) found evidence that

females who received either nalbuphine and butorphanol, kappa-opioid agonists, experienced significantly greater analgesic efficacy than males. The investigators found a significant main effect for nalbuphine, $F(8, 208) = 2.4$, $p = .02$, and butorphanol, $F(8, 144) = 17.5$, $p < .001$, with females experiencing greater analgesic efficacy than males. The biochemical basis for the significantly greater analgesic efficacy of kappa-opioid agonists reported in female participants is not understood. Female participants were compared based on the day in their menstrual cycle at the time of tooth extraction, but this comparison failed to describe any difference for either drug. A pharmacokinetic cause was dismissed by the investigators after no differences were found in the incidence of reported side effects between male and female participants. However, the investigators postulated that the more limited duration of analgesia experienced by male participants may suggest male androgen antagonism, a sex difference (Gear, Miaskowski et al., 1996).

In a follow-on study using the kappa opioid agonist pentazocine, female participants were compared for differences between analgesic efficacy and the day of their menstrual cycle following the extraction of an impacted molar tooth. No significant differences were found in this comparison. The investigators suggested that differences observed in females may be related to progesterone or estrogen potentiation of the kappa opioids and males may have experienced a reduced level of analgesia as a result of an unknown negative testosterone interaction, or both of these sex-dependent mechanisms occur (Gear, Gordon et al., 1996). Human studies remain inconclusive with some supporting (Hellstrom & Lundberg, 2000) and others unable to provide significant evidence (Gear, Gordon et al., 1996; Gear, Miaskowski et al., 1996; Zeichner, Loftin, Panopoulos, Widner, & Allen, 2000) that pain is reduced in females during a specific phase in their menstrual cycle where hormone levels may help explain sex differences. Gender differences, or those differences based on role differences, cultural expectations,

experiences, and other variables that influence masculinity and femininity may help explain pain threshold and tolerance.

In a cold pressor study conducted by Zeichner, Loftin, Panopoulos, Widner and Allen (2000), participants completed the Parameters of Pain Questionnaire-Revised. Females reported greater frequencies of pain episodes, $F(1, 41) = 9.22$, $p < .05$, and higher pain symptom intensity, $F(1, 41) = 4.79$, $p < .05$. Contrary to the data obtained on the questionnaire suggesting a significant gender difference, the investigators found that pain ratings (on an 11-point pain rating scale) between male and female participants did not significantly vary when subjected to the experimental conditions of the cold pressor test. The investigators concluded that the experimental milieu may have contributed to the lack statistical significance in female pain ratings or that hormonal influences may have had an impact on pain threshold and tolerance. Hormone levels were not assayed and the collection of data did not include phase or day in the menstrual cycle (Zeichner et al., 2000).

Otto and Dougher (1985) investigated whether sex (male and female) differences and personality factors influence responses to pain. Forty males and 40 females completed two surveys, the Marlowe-Crowne Social Desirability Scale and Bem Sex-role Inventory. Masculinity-femininity (Bem T-scores) are considered masculine if less than 50 and feminine if greater than 50. While the investigators reported a statistical significant correlation for masculinity-femininity and pain threshold, data actually suggests only a weak correlation ($r = -0.31$, $p < 0.03$). Pain tolerance was significantly longer in males ($M = 172.6$ s) than females ($M = 102.6$ s). However, masculinity-femininity and social desirability scores were not predictive of pain tolerance when the effect of sex, male or female, was controlled. The investigators reported a significant main effect for the effect of sex on pain tolerance after controlling for masculinity-femininity and social desirability. They further suggested that since the majority of variance in pain threshold and tolerance were attributed to sex alone, personality or

conditioning factors and structural or physiologic differences may have influenced the results (Otto & Dougher, 1985). The evidence here suggests that gender-associated influences partially predict pain threshold, with a note of caution that the magnitude is uncertain and highly individual.

Summary

There is evidence in rodent studies using thermal (Ghorpade & Advokat, 1994; Mao, Price, Hayes et al., 1992; Meller et al., 1996; Woolf, 1983), chemical (Haley et al., 1990; Ma & Woolf, 1995), mechanical (Woolf & Thompson, 1991), or electrical (Ma & Woolf, 1995) evoked hyperalgesia that the NMDA receptor is integral in both the establishment and maintenance of central sensitization. Evidence from animal studies demonstrate that competitive and non-competitive NMDA receptor antagonists inhibit central sensitization (Ghorpade & Advokat, 1994; Haley et al., 1990; Ma & Woolf, 1995; Mao, Price, Hayes et al., 1992; Mao, Price, Mayer et al., 1992; Meller et al., 1996; Woolf, 1983) and tolerance to morphine sulphate (Andersen et al., 1996; Bharagava & Zhao, 1996; Bovill, 1997; Elliott et al., 1994).

Human studies have had mixed results using the NMDA antagonist, Dextromethorphan, with evidence supporting the reduction in postoperative pain following DM administration (Wu et al., 2000) and others (Kauppila et al., 1995) unable to demonstrate a significant difference between DM and control groups. Ketamine studies have added evidence that preoperative ketamine bolus (Fu et al., 1997; Roytblat et al., 1993), bolus plus intraoperative low dose infusions (Arendt-Nielsen et al., 1995; Stubhaug et al., 1997) and post-stimulus bolus plus infusion (Andersen et al., 1996) have demonstrated a reduction in total postoperative analgesic doses and longer intervals of pain and lower pain scores. Ketamine has activity at the mu receptor (Sarton et al., 2001), which may be its primary analgesic mechanism. There are many unanswered questions regarding sex differences in pain control regimens, including the utility of ketamine.

Gender and sex differences have been explored with some (Hellstrom & Lundberg, 2000) generating evidence that there are sex-dependent differences in pain modulation that varies with estrogen levels and others unable to demonstrate a difference (Zeichner et al., 2000). What was clear is that males demonstrate higher pain tolerance to cold pressor tasks; however, threshold may be increased during the luteal phase of the menstrual cycle (Otto & Dougher, 1985). The extent to which sex and gender influence the pain experience is limited in current research and there is lack of consensus about the influence of hormonal milieu on pain.

This compilation of evidence suggest that ketamine has clinical utility to both inhibit central sensitization through the NMDA receptor and provide direct analgesia through the mu receptor. Evidence (Fu et al., 1997) suggesting reductions in total narcotic consumption of up to 40% in the first 24 hr postoperative period are striking and provide a compelling reason to move forward with this study. The relevance this study has to anesthesia is the potential to discover a gender-specific ketamine dose which may prove more efficacious in meeting the demands of post-surgical pain control, reducing PACU time, reducing inpatient length of stay, and improving patient satisfaction.

CHAPTER III

Methodology

The purpose of this research was to provide answers to two questions: (1) was the combination of propofol plus ketamine delivered as a low dose perioperative infusion more efficacious than propofol alone on postoperative pain perception in laparoscopic surgical patients and (2) was a low dose perioperative infusion of propofol plus ketamine more efficacious in males compared to females? The study design was a double-blind, 2 X 2 factorial design. The study's protection of human subjects, design, instrumentation, data analysis and sample will be developed in this chapter.

Population, Sample, and Setting

The population of interest for this study was the patients scheduled to undergo laparoscopic surgery at William Beaumont Army Medical Center, El Paso, Texas. A convenience sample was drawn from the body of authorized beneficiaries.

The convenience sample was composed of male and female subjects between the ages of 18 and 65 years who had legal capacity and competency to give consent for participation in research. The patients were classified according to the American Society of Anesthesiologists (ASA) category I, II, and III.

The study excluded patients that have bleeding disorders, history of hepatitis, allergy to ketamine, chronic or acute liver disease, history of major/severe affective and/or anxiety disorder, recent or long term alcohol/narcotic abuse, cancer, history of HIV infection, or pregnant females. In addition, patients who had taken dextromethorphan (DM) within 24 hours of the scheduled surgical procedure were likewise excluded. DM is known to effect the NMDA receptor which could lead to skewed data.

An appropriate sample size for this study was N=68, with 17 participants in each of four subgroups. This number was partially derived from a power analysis using a medium effect size (f^2) of 0.35, alpha = 0.05, and a power of 0.80. The formula suggested

by Cohen (1998), $n_c = (n' - 1)(u + 1)$/number of cells + 1, was used to determine the number of participants per cell (n_c). The table value n' was extracted using a medium effect size of 0.35, power of 0.80, and (u) algebraically defined as the difference between two groups minus one degree of freedom (u = 1).

The effect size was derived from analysis of ketamine studies (Andersen et al., 1996; Roytblat et al., 1993) which used experimentally-induced and surgical pain in human models. In a capsaicin-induced pain study conducted with 17 male and female participants using a ketamine bolus of 0.2-mg/kg followed by infusion of 5-mcg/kg/min, Andersen et al. (1996) found a medium effect size of 0.32 for the magnitude of NMDA receptor influence on increased spinal excitability. Roytblat et al. (1993) demonstrated a large effect size of 15.36 for total morphine consumption in the first 24 hours following open cholecystectomy (N = 22 females). Additionally, a large effect size of 3.57 was found for time to first request for analgesic medication in the same population. It is likely that the effect size for our proposed study lies somewhere between medium and large based on these *post hoc* comparisons. We believed that the magnitude of the large effect sizes demonstrated in the latter study (Roytblat et al., 1993) together with a mid-range medium effect size in the former study (Andersen et al., 1996) provided a compelling reason to weight the range of the medium effect size (0.25 to 0.39) described by Cohen (1998); therefore, we used 0.35 for this study.

Gender is a blocking variable as it is an independent variable that can not be manipulated. Therefore, men and woman were randomly assigned to experimental and control groups separately. This method increased our study's precision and enhanced the likelihood of detecting a difference between the experimental (ketamine and propofol) and control groups (propofol alone) (Cohen, 1998; Polit & Hungler, 1999).

Instrumentation

Visual Analogue Scale (VAS).

Quantification of pain was measured using a horizontal version of the 100 mm VAS (Appendix E) anchored with the words "no pain" at the same level as the 100 mm horizontal line immediately outside the left vertical line stop and "worst pain possible" at the same level as the horizontal line immediately outside the right vertical line stop. The VAS instrument length was checked to ensure each is 100 mm after photocopy reproduction.

The VAS instrument is not immediately intuitive to all participants; therefore, standardized participant education using the VAS Instruction Protocol (Appendix F) was conducted to enable accurate pain scoring. Each participant was instructed, by an investigator preoperatively and again by a postanesthesia care unit (PACU) nurse postoperatively, to draw a vertical line with a pen across the horizontal line of the 100 mm VAS that corresponded with the level of pain they were immediately experiencing. The anchored ends of the scale were initially pointed out, read aloud to the participants, and reinforced as necessary. After the subjects marked the scale, a study investigator or PACU nurse then checked the 30 minute, time to first request, or PACU discharge block and recorded the time. VAS scoring was accomplished using a 100 mm grid overlay, recording pain scores to the nearest two millimeters. The VAS has advantages and limitations relevant to its selection as the tool to measure pain in this study.

The reliability of the VAS used to measure pain scores in patients who underwent extraction of impacted third molars has been reported (Seymour, 1982). The sample consisted of six male and six female subjects between the ages of 19 and 25 years old. Each subject underwent two surgeries spaced by at least a four-week interval to remove impacted third molars. An analgesic treatment of 600-mg or 1200-mg of aspirin or placebo was administered. The investigator used a second visual analogue scale to establish reliability and validity of the first VAS. The correlation coefficient (r = .956,

$p < .001$) was obtained comparing pain ratings between the two instruments. Polit and Hungler (1999) suggest a conservative reliability coefficient of at least ($r = .90$) when the measurement data will be used to make clinical decisions.

Seymour (1982) also made comparisons of sensitivity between the following three instruments: (a) VAS, (b) 4-point descriptive scale, and (c) 11-point numerical rating scale (NRS). The investigator described typical dental pain intensity ranging from mild to moderate and suggested that the 4-point descriptive scale was least sensitive to small changes in pain intensity secondary to its design, offering the subject only four points. The author stated that the 11-point NRS has more sensitivity than the 4-point scale, but these two instruments lack sufficient sensitivity to discriminate between small changes in a subject's pain intensity. The lack of sensitivity found in scales with fewer points is supported by similar research (Joyce, Zutshi, Hrubes, & Mason, 1975; Machin, Lewith, & Wylson, 1988; Scott & Huskisson, 1976). This point is salient to choosing an instrument for measuring pain that allows a subject to accurately report his or her pain.

Seymour (1982) found both construct and criterion-related validity in the VAS. To discern construct validity, subjects were randomized to receive one of two aspirin doses. Those who received aspirin recorded decreasing pain scores on the VAS. In a criterion-related approach, the investigator used an established criterion instrument, the NRS, and compared it to the VAS and found a high correlation coefficient, $r = .91$ between instruments. While this correlation coefficient exceeds the criteria ($r = .9$ or greater) recommended by Polit and Hungler (1999), the VAS by design provides only a one-dimensional pain assessment and fails to discriminate between the sensory-intensity (magnitude) and affective dimensions (unpleasantness) of the pain experience (Duncan, Bushnell, & Lavigne, 1989).

In consideration of these advantages and limitation of the VAS and the needs of this study to use an instrument capable of detecting small differences in pain intensity between men and women, and between women at different points in their menstrual

cycle, the investigators of this study elected to use the VAS. The VAS was also familiar to PACU nurses at William Beaumont Army Medical Center where this study was carried out and this may have improved inter-rater reliability and ease of use in collection of data.

Demographic Data Sheet.

A demographic data sheet (Appendix C) was recorded for each study participant, which contained the following information: sex, age, height, weight, date of last menstrual period, oral contraceptive or hormone replacement therapy (estrogen), surgical procedure, ASA category, and surgeon. Menstrual cycle data was collected and analyzed for analgesic sex differences following ketamine administration together with hormone fluctuations associated with the follicular (including menses) phase, ovulation, and the luteal phase.

Data Collection Sheet.

A data collection sheet (Appendix D) was used to record the following participant data: (a) opioid analgesic use for the 24 hour period following the discontinuation of the propofol/saline or propofol/ketamine solution, (b) time to first request for pain medicine, (c) ketamine related side effects, and (d) the total amount of local anesthetic used by the surgeon intraoperatively. The collection of VAS scores at four time points, time to first request for an analgesic, and total opioid analgesic use for the 24 hour period allowed triangulation for a more accurate analysis of the results. Four VAS instruments, the demographic data sheet, and data collection sheet became part of the participant's research file that was secured in a locked filing cabinet in a room that was locked when the PI and AI(s) were not present. These instruments were labeled only with the participants study number to maintain anonymity and confidentiality.

Procedure for Data Collection

The female participants were assigned consecutive numbers (1-42) when enrolled and males were assigned consecutive numbers (43-84). No other identifying data

appeared on the data collection sheet. A separate master table (secured by the PI) listing the hospital identification number allowed for the tracking of patients. Participants were randomly assigned separately by sex to either the experimental or control group where the participants received propofol with ketamine or propofol with preservative free saline respectively.

By convention for preemptive analgesia, a small dose (defined as less than induction doses i.e. less than 2-mg/kg) of ketamine was mixed in a solution with propofol. Propofol is commercially available as a 10-mg/ml concentration while ketamine is commercially available as a 100mg/ml concentration. In this study, participants were randomly assigned to receive an intravenous induction dose of propofol 1 to 2-mg/kg followed by an infusion of either: (a) propofol 200-mg (20 cc) mixed with preservative free saline (0.5 cc), or (b) propofol 200-mg (20 cc) mixed with ketamine 50-mg (0.5 cc) prior to surgical insult. For convenience, these solutions will henceforth be termed propofol/additive solutions. The infusion dose was calculated to deliver 12.5-mcg/kg/min of the propofol/additive solution which was administered as a perioperative infusion. The propofol/additive solution was discontinued 30 minutes prior to the end of surgery. Therefore, the experimental group received 3.125-mcg/kg/min of ketamine perioperatively. Thus, a hypothetical 70 kg individual did not receive more than 52-mg of ketamine with an operative time less than or equal to 4 hours. If a clinical scenario presented involving extremes in operative time and/or weight, the propofol/additive solution was discontinued before the end of surgical manipulation to maintain (1) the total dose of ketamine no greater than 100-mg and (2) the weight-based dose of ketamine below 2-mg/kg.

The investigators were blinded to the contents of the propofol/additive solutions. The OR pharmacy technician prepared the propofol/additive solutions. The solutions was checked by the staff CRNA or MD. The investigators administered the anesthetic to the

study participants; therefore, in order to control for bias, particularly the total amount of fentanyl administered to participants in each group, it was prudent to have the investigative team blinded.

A standard anesthesia protocol was followed. After appropriate preoperative evaluation and establishment of intravenous access, patients received midazolam 1 to 3-mg in the preoperative holding area. Induction occurred with fentanyl 100 to 250-mcg (not to exceed this dose prior to incision), rocuronium 0.5 to 0.7-mg/kg, and 1 to 2-mg/kg of propofol. Immediately after securing the airway, the investigator initiated the propofol/additive solution infusion. General anesthesia was maintained with fentanyl 3 to 4-mcg/kg/hr (not to exceed a total perioperative dose of 4-mcg/kg/hr, including the induction dose), isoflurane, nitrous oxide (N_2O), and rocuronium titrated to effect. The propofol/additive solution was terminated 30 minutes prior to end of surgery. Zofran 4-mg was administered postoperatively prior to patient transport to the PACU.

Protection of Human Subjects

The investigators sought permission from the Institutional Review Board at William Beaumont Army Medical Center and from the University of Texas Health Science Center at Houston to conduct a study on human subjects. The investigators counseled all subjects and attempted to obtain informed consent at least one day prior to the procedure to ensure the integrity of the volunteer nature of participation.

The informed consent counseling session fully respected the capacity of consent. Following the counseling, the investigators ensured that the patient had a working knowledge of the research to include risks and benefits. The participants understood the purpose of the study, nature of participation, time commitment and their right to withdraw at anytime before or during the research protocol. A participant's right to privacy was enforced by maintaining records in a secure file cabinet in a secured room.

Study Design

This study was a double-blind, 2 X 2 factorial design. Participants were randomized to one of two treatment groups. The inclusion of male and female subjects was intentional to block for gender. This design was selected as it provides for testing of more than one hypothesis. There were two hypotheses being tested in this study. A discussion of threats to internal and external validity follows and is necessary to describe both threats and control measures which protected the study from extraneous variables. The types of threats to internal and external validity in this study are defined by Polit and Hungler (1999).

Internal Validity Threats

Selection is a challenge to internal validity in this study for several reasons. First, the study participants could feasibly be randomly selected from the relatively small population of William Beaumont Army Medical Center's laparoscopic patients. The finite data collection period, together with a limited number of patients undergoing laparoscopic surgery per week, pointed toward using a convenience sample and random assignment. Therefore, each laparoscopic patient who met inclusion criteria were given an opportunity to participate. Second, female laparoscopic patients who met inclusion criteria were possibly at different phases in their menstrual cycle. Randomizing all subjects to treatment groups controlled for this variability; however, it may not have eliminated the chance of having non-equivalent groups. For example, the distribution of female participants may have been skewed with regard to the phase in their menstrual cycle.

Maturation presented a challenge to internal validity in that subjects may have rated pain scores lower, requesting or self-administering less medication as a function of elapsed time rather than a treatment effect of ketamine alone. Furthermore, after subjects were discharged, it is not inconceivable that some may have self-medicated with over-the-counter or old prescription analgesics. A decision to limit the postoperative period to

24 hours after the discontinuation of the propofol/saline or propofol/ketamine infusion was made to control the magnitude of this threat.

Instrumentation posed another threat to internal validity. The baseline measure taken before surgery is perhaps the easiest measure compared to those taken in the postoperative period. The choice of general anesthesia using a balanced anesthetic may have affected the participants' ability to accurately mark the VAS. Drowsiness in the immediate postoperative period, decreased visual accommodation, shivering, weakness and coordination problems, and intravenous catheters placed in the dominant hand have been suggested to add a level of error when using the VAS (Murphy, McDonald, Power, Unwin, & MacSullivan, 1987). There has been at least one report that an overestimation of pain may occur if subjects do not see their previous scores (Scott & Huskisson, 1979). Participants who were unable to complete the VAS, described as a failure rate up to 11%, has been reported in the literature. Investigators suggested that the subjects who were unable to complete the VAS were older and may have decreased ability to think and process abstractly, as required to use the VAS (Kremer, Atkinson, & Ignelzi, 1981). Controls included staff training to increase awareness of potential error during the immediate postoperative period, teaching the patient about the VAS, practicing its use in the preoperative period, and limiting the age range (18 to 65 years old). Exclusion of potential participants with major/severe affective and/or anxiety disorder, long term alcohol and/or narcotic abuse, and patients with chronic and acute liver disease provided additional control.

External Validity Threats

The population available was military members, their beneficiaries, and retired military members living at or within the service or catchment area of William Beaumont Army Medical Center. A convenience sample of 18 to 65 year old adult laparoscopic patients was taken from this largely healthy population which imposed limitations on generalizability. Female participants in this population were at different days in their

menstrual cycle, some were taking oral contraceptives or estrogen replacement therapy. Estradiol levels were not measured, which also limits data interpretation and extrapolation.

A novelty effect may have occurred. Participants were informed, according to the approved protocol, that they were randomly assigned to one of two treatment groups. Despite prestudy counseling about the random assignment, participants may have believed they had been assigned to receive the experimental drug and demonstrate behavior that suggested a treatment effect. Our randomized, double-blind study decreased this threat.

Experimenter effects may overtly influence participants' behavior. Controls to decrease this threat included matter-of-fact instructions on the purpose of the study, use of the VAS, and postoperative pain medicine availability. Investigators, PACU nurses, and ward nurses used the standardized VAS instruction protocol (Appendix F) to control for variability in teaching patients how to use the VAS. The protocol prohibited defining points along the VAS for the participants.

Measurement effects can confound the VAS. The VAS requires a two-step process. First, the participants marked their perceived pain score along the 100 mm VAS. Then, the investigators used a scoring grid overlay exactly the same length as the VAS. Each VAS was measured and verified. To control for measurement effects, the reproduction process included a quality control measurement verification step which determined the length of each VAS. Reproduced VAS pain scales not measured at exactly 100 mm were discarded.

Procedure for Data Analysis

There are several positions taken by researchers with respect to the level of data provided by the 100 mm VAS. Herr and Mobily (1993) tested the VAS and Verbal Descriptor Scale (VDS) separately for homogeneity and found that the ranks were not normally distributed. Chapman et al. (1985) stated that rating scales are rank ordered with

undefined category boundaries that may not be equal in interval. The authors further state that an assumption of equal intervals is questionable unless sufficient evidence exists that the participant is treating the categories as equal intervals.

Campbell and Lewis (1990) argue that data skewed at either end of the VAS may be transformed using arcsin transformation and meet the criteria for parametric testing. Lee and Kieckhefer (1989) counter the previous argument that the VAS is a rank-ordered scale (Chapman et al., 1985), stating that the VAS has increased sensitivity due to its freedom from previously quantified intervals, and that the VAS produces quantifiable, interval-level data. The researchers further state that VAS allows subjects to make fine discriminations in pain scores and, as such, a greater variance in responses which facilitates a normal distribution, a criteria for parametric testing. The VAS has been validated as ratio level data in a human model of chronic and experimentally-induced pain (Price, McGrath, Rafil, & Buckingham, 1983). We will treat VAS data as interval level data in this study using the repeated measures ANOVA statistic to analyze pain scores. The decision is made *a priori* to compare male and female pain ranks separately.

The experiment will yield two forms of parametric data, total mg use of opioid for analgesia for the 24 hour period beginning at the time the propofol/saline or propofol/ketamine infusion is discontinued, and time in minutes to first request for an analgesic medication. Parametric data will be analyzed using the 2 X 2 Factorial ANOVA. This statistic provides a method of analyzing the difference among the means of three or more independent groups (Polit & Hungler, 1999).

CHAPTER IV

Analysis of Data

The analyzed data from this study is presented in the following five sections: (a) a description of the selected statistical methods, (b) demographic data analysis comparing the experimental and control groups on the basis of age, height, weight, surgical time, total local anesthetic dose administered, total intraoperative fentanyl dose, ASA physical status, and type of surgery performed, (c) analysis of time to first request for analgesic medication in the postoperative period starting when the study infusion was discontinued and limited to the first 24 hours, (d) analysis of the total 24 hour opioid equivalent dose, and (e) analysis of Visual Analogue Scale pain scores within and between groups.

The goal of this study was to explore differences in postoperative pain perception between males and females using three measurements: (a) time to first request for analgesic medication, (b) total 24-hour opioid equivalent dose, and (c) visual analogue scale (VAS) pain scores to triangulate data following a perioperative low dose ketamine infusion at 3.125 mcg/kg/min or saline. A standardized balanced general endotracheal anesthetic (Appendix B) was administered. The study design was an experimental, 2 X 2 factorial, controlled study with double-blinding and random assignment. A convenience sample of patients undergoing laparoscopic general and gynecologic surgical procedures who gave informed consent were included in the study at William Beaumont Army Medical Center in El Paso, Texas.

Interval level demographic data including height, weight, age, surgical time, total local anesthetic dose, and total intraoperative fentanyl dose were analyzed using the ANOVA statistic after determination that the population was normally distributed and that there was homogeneity of variance between and within groups. Ordinal level data including participants' sex, American Society of Anesthesiologists Physical Status classification, and type of surgery were analyzed using the chi-square ($\chi 2$) statistic. Tables 1 through 3 are representative of these several descriptive statistical analyses.

Table 1

Descriptive statistics for population studied

KETAMINE	SEX		HEIGHT (inches)	WEIGHT (kg)	AGE	SURGICAL TIME (min)	LA DOSE (mg)	INTRAOP FENTANYL (ME)
Ketamine	Female	Mean	62.83	78.53	39.28	93.94	70.00	38.4722
		N	18	18	18	17	5	18
		Std. Deviation	2.036	14.685	11.955	25.601	22.079	8.83421
	Male	Mean	69.13	81.50	46.25	98.13	120.00	46.2500
		N	8	8	8	8	1	8
		Std. Deviation	1.727	12.884	15.126	49.238	.	16.63688
	Total	Mean	64.77	79.45	41.42	95.28	78.33	40.8654
		N	26	26	26	25	6	26
		Std. Deviation	3.525	13.967	13.115	33.883	28.402	11.99880
Saline	Female	Mean	63.13	76.68	33.42	85.81	83.33	38.4737
		N	19	19	19	16	3	19
		Std. Deviation	3.487	15.549	13.167	30.520	57.735	13.37335
	Male	Mean	68.50	92.30	43.00	107.22	50.00	46.5000
		N	10	10	10	9	1	10
		Std. Deviation	1.841	10.678	10.832	35.340	.	15.99479
	Total	Mean	64.98	82.07	36.72	93.52	75.00	41.2414
		N	29	29	29	25	4	29
		Std. Deviation	3.956	15.784	13.063	33.294	50.000	14.56980
Total	Female	Mean	62.99	77.56	36.27	90.00	75.00	38.4730
		N	37	37	37	33	8	37
		Std. Deviation	2.839	14.954	12.766	27.953	35.757	11.23731
	Male	Mean	66.78	87.50	44.44	102.94	85.00	46.3889
		N	18	18	18	17	2	18
		Std. Deviation	1.768	12.618	12.613	41.317	49.497	15.79329
	Total	Mean	64.88	80.83	38.95	94.40	77.00	41.0636
		N	55	55	55	50	10	55
		Std. Deviation	3.725	14.874	13.180	33.257	35.839	13.29510

There were 57 adult participants that were recruited into this study, distributed as 37 females and 20 males. Two male subjects were lost to attrition due to an unanticipated difficult airway requiring necessary interventions outside the standard protocol and the conversion of one laparoscopic to open cholecystectomy. Statistical analysis was done using the data of the remaining 55 participants. ANOVA statistical analysis of demographic data in Tables 1 and 2 demonstrated there were no statistically significant differences between groups in height, weight, age, surgical time, total local anesthetic dose, and total intraoperative fentanyl dose.

Table 2

Descriptive statistics for associated covariates. No significant findings

			Sum of Squares	df	Mean Square	F	Sig.
HEIGHT * KETAMINE	Between Groups	(Combined)	.625	1	.625	.044	.834
	Within Groups		748.857	53	14.129		
	Total		749.482	54			
WEIGHT * KETAMINE	Between Groups	(Combined)	94.307	1	94.307	.422	.519
	Within Groups		11852.847	53	223.639		
	Total		11947.153	54			
AGE * KETAMINE	Between Groups	(Combined)	302.697	1	302.697	1.767	.189
	Within Groups		9078.139	53	171.286		
	Total		9380.836	54			
SURGTIME * KETAMINE	Between Groups	(Combined)	38.720	1	38.720	.034	.854
	Within Groups		54157.280	48	1128.277		
	Total		54196.000	49			
LADOSE * KETAMINE	Between Groups	(Combined)	26.667	1	26.667	.018	.895
	Within Groups		11533.333	8	1441.667		
	Total		11560.000	9			
INTRAOP ME * KETAMINE	Between Groups	(Combined)	1.938	1	1.938	.011	.918
	Within Groups		9543.089	53	180.058		
	Total		9545.027	54			

Groups were equivalent with regard to ASA physical status category, surgical procedure, and sex (Table 3). These data were analyzed using the chi-square statistic and Fischer's exact test. There were only two ASA 3 participants, therefore their data were collapsed into the ASA 2 group. By convention, cells are expected to have at least 5 observed frequencies to demonstrate normal distribution about the population value. The integrity of collapsed data is preserved under the premise that group reassignment did not alter assignment to the experimental or control group.

Table 3

Distribution by sex, ASA status and group. No significant findings

SEX				KETAMINE		Total
				Ketamine	Saline	
Female	ASA	1	Count	5	6	11
			Expected Count	5.4	5.6	11.0
		2	Count	13	13	26
			Expected Count	12.6	13.4	26.0
	Total		Count	18	19	37
			Expected Count	18.0	19.0	37.0
Male	ASA	1	Count	2	5	7
			Expected Count	3.1	3.9	7.0
		2	Count	6	5	11
			Expected Count	4.9	6.1	11.0
	Total		Count	8	10	18
			Expected Count	8.0	10.0	18.0

Data was next analyzed to ensure the requirements for parametric testing were met. The first requirement is that the sample be randomly drawn from the population or randomly assigned. The sample was a convenience sample and random assignment of participants was done using a table of random numbers by the pharmacist at William Beaumont Army Medical Center. The second requirement is normal distribution of data. The Shapiro-Wilkes test was used and demonstrated that all data was normally distributed. Levine's test of homogeneity demonstrated that 24-hour opioid equivalent dose and VAS data were homogenous; however, time to first request data was not.

Cohen (1998) suggests transforming data to meet the assumption of homogeneity and by convention data was transformed using the inverse log, analyzed, and the variances found to be homogenous. Time to first request data then met the assumptions for parametric testing. The following section describes the analyses of the dependent variables examining differences in postoperative pain perception in males and females

who received ketamine or saline and whether sex differences were evident on the basis of hormonal milieu.

Findings

Time to first request for analgesic medication, total 24-hour opioid equivalent dose, and visual analogue scale pain scores were collected to determine if postoperative pain perception following low dose ketamine is altered selectively in males or females. We hypothesized that groups receiving ketamine and males would have an increased time to first request for analgesic medication, a reduced total 24-hour opioid equivalent dose and decrease pain scores on the 100 mm VAS. The first two independent variables, TTFR and total 24-hour opioid equivalent dose is interval level data and was analyzed using the ANOVA statistic. The visual analogue scale pain scores were treated as interval level data and analyzed using the repeated measures ANOVA.

Data in Figure 2 represents the analysis of time to first request for analgesic medication. There were no significant differences ($p > .05$) between groups or by gender. Paradoxically, males who received ketamine (mean time to first request = 52 minutes) had a 65 minute mean increase in time to first request compared to males who received saline (mean time to first request = 117 minutes). This difference in TTFR however, did not reach statistical significance.

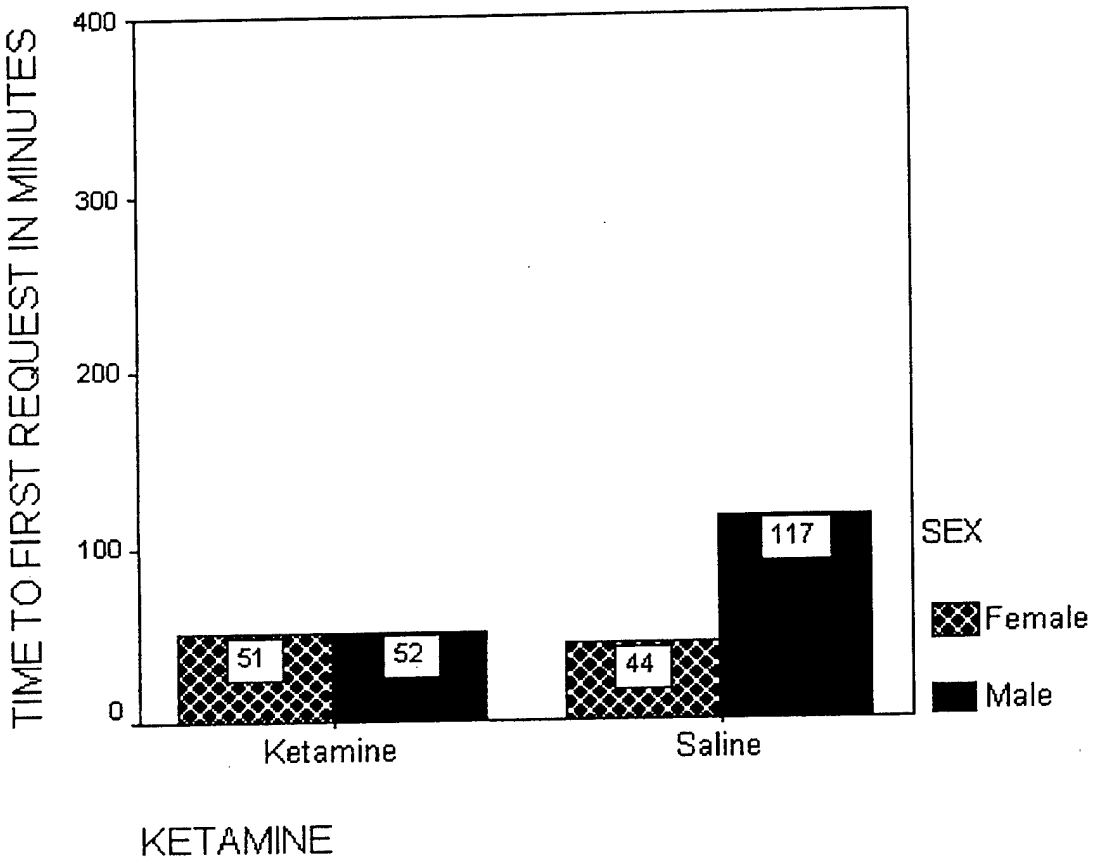

Figure 2. Time to first request for analgesic medication in males and females following ketamine or saline administration. No statistically significant differences were found among the groups.

Total 24-hour opioid equivalent dose was used as an additional measure of postoperative pain perception where higher consumption may represent increased pain perception. Total 24-hour opioid equivalent data was collected starting at the discontinuation of the study infusion of ketamine or saline and stopped 24 hours later. The collection of these data were accomplished with preaddressed, postage paid mail-in surveys with written instructions to provide a 24 hour record of each dose of analgesic medication. The total 24 hour opioid equivalent dose survey return response rate was 80% for females and 94% for males. Two females' data were characterized as extreme outliers and removed from the final statistical analysis leaving 28 females and 17 males.

Total 24-hour opioid equivalent dose ANOVA analysis demonstrated that there was no statistically significant difference ($p > .05$) between males and females who received ketamine or saline. In contrast to the 65 minute mean decrease in time to first request reported by males who received ketamine, the trend was such that males who received ketamine reported less total 24-hour opioids consumption (mean = 13 mg) compared to males who received saline (mean = 16 mg). Figure 3 illustrates these findings.

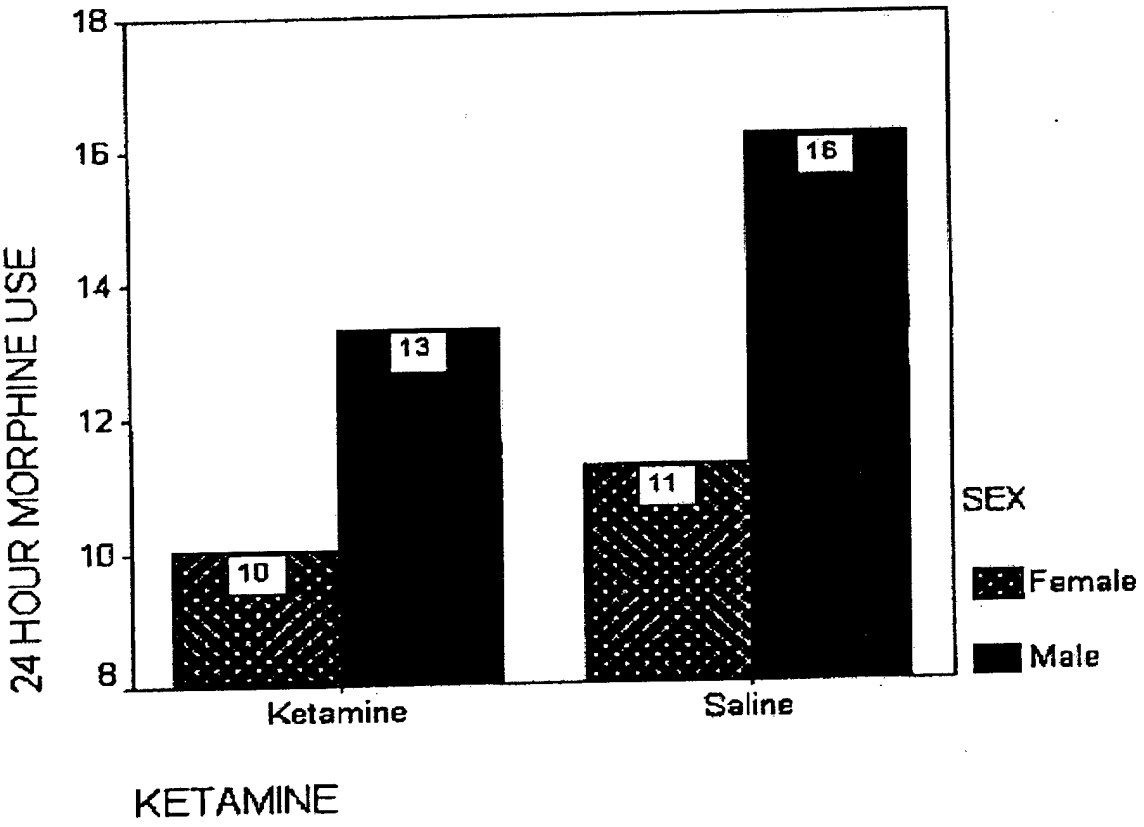

Figure 3. 24-hour opioid (or its equivalent) use in males and females following ketamine or saline administration. No statistically significant differences were found among the groups.

Pain was assessed at 4 previously determined intervals during the first 24 hours using the 100 mm VAS. These intervals were: (a) time to first request for analgesic medication, (b) 30 minutes after arrival in the PACU, (c) discharge from the PACU, and (d) 24 hours following discontinuation of the study infusion (Figure 4), to determine if there was a late effect that may be related to intraoperative ketamine administration. The 30 minutes after arrival in PACU and 24 hour intervals were fixed chronologically, while the time to first request for analgesic medication interval and PACU discharge were not fixed. VAS data collected at the 24-hour interval was most frequently obtained using a mail-in 24 hour VAS. A mail-in survey queried the 24-hour 100mm VAS pain score of participants and yielded a survey return response rate of 81% for female participants and 89% for male participants.

Visual Analogue Scale pain scores were compared using the repeated measures ANOVA. Time interval plots reflect mean VAS pain scores at TTFR, 30 minutes after PACU arrival, PACU discharge, and 24 hours following discontinuation of ketamine or saline. There were no statistically significant differences between groups who received ketamine or saline. An expected reduction in pain scores for all groups is apparent.

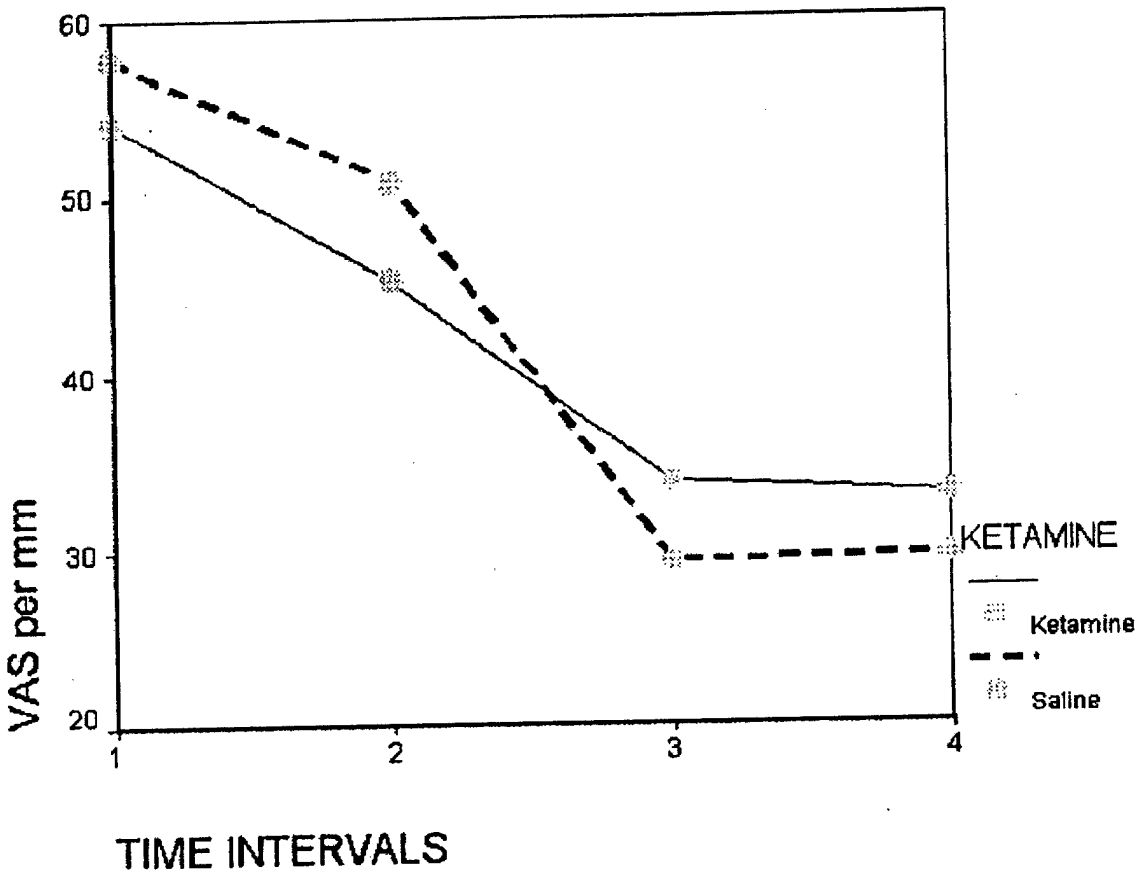

Figure 4. Repeated measures VAS in males and females following ketamine or saline administration. Time interval 1 = TTFR, 2 = 30 minutes after PACU arrival, 3 = time PACU discharge, and 4 = 24 hours following discontinuation of ketamine or saline. No statistically significant differences were found among the groups.

Finally, *a priori* we planned to examine the data with regard to hormonal milieu. Therefore, date of last menstrual period, birth control pill use, and hormone replacement therapy including estrogen or estrogen/progesterone regimens, previous oophorectomy, and post-menopausal status were all collected during the initial interview prior to surgery. Participants were assigned into one of three groups on the basis of hormonal milieu. Females who were within the first 14 days of their self-reported first day of last menstrual period (follicular phase) on the day of surgery or taking estrogen replacement therapy were categorized as the follicular phase group (estrogen unopposed). Females who were

on day 15-28 (luteal phase) of their self-reported first day of last menstrual period on the day of surgery or those females taking an estrogen/progesterone birth control pill combination or estrogen/progesterone hormone replacement therapy were categorized as the luteal phase group (estrogen opposed). Males and females not taking any hormone replacement who self-reported that they were post-menopausal or had previously undergone oophorectomy were categorized as the "no hormone" group.

Time to first request for analgesic medication was analyzed using the Kruskall-Wallis statistic because data did not meet the assumptions for parametric data analysis. There was a significant difference ($p < .05$) in mean time to first request for analgesic medication for females in the follicular phase group who were administered ketamine compared to females administered ketamine in the luteal phase group such that females in the luteal phase group had a significantly longer time to first request for analgesic medication (mean = 63 minutes) than those in the follicular phase group (mean = 33 minutes). A prolonged time to first request is thought to represent an increase in pain threshold. Time to first request for analgesic medication among groups identified by hormonal milieu is illustrated in Figure 5.

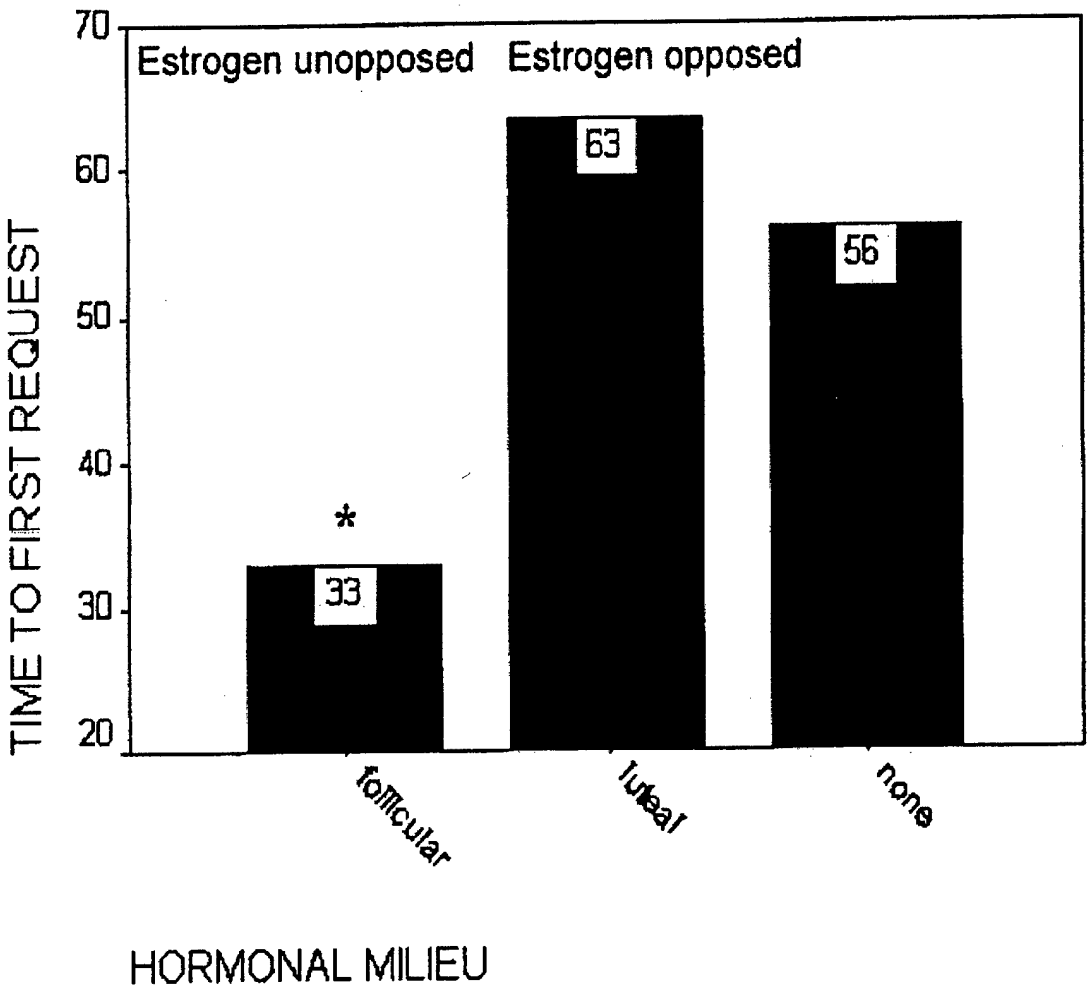

Figure 5. Time to first request for analgesic medication as a function of hormonal milieu. *Significantly different versus luteal phase group ($p < 0.05$).

Last, total 24-hour opioids equivalent dose was compared using a 2 X 3 ANOVA statistic by group on the basis of hormonal milieu. There were no statistically significant differences ($p > .05$) among groups. A trend showing reduction in total 24-hour opioid equivalent dose, which followed the direction demonstrated in TTFR data for females in the luteal phase, was suggested (Figure 6).

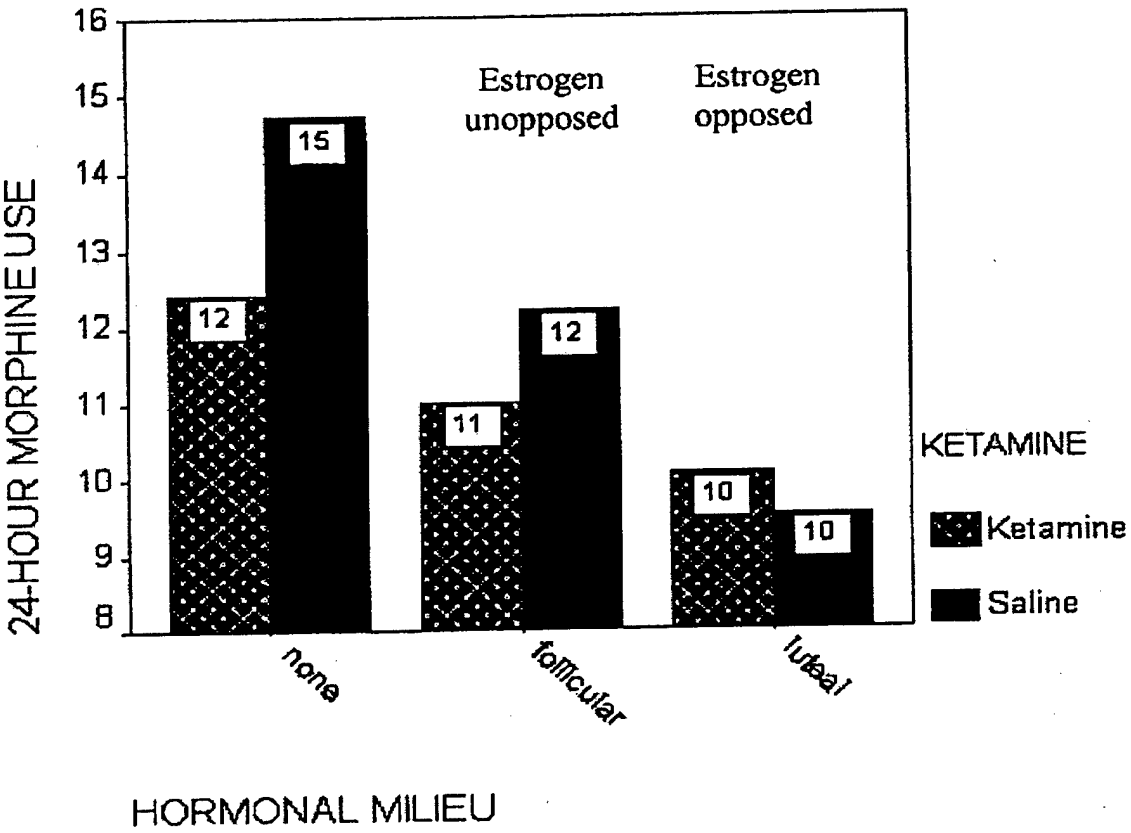

Figure 6. Total 24-hour opioid equivalent dose as a function of hormonal milieu. There were no statistically significant differences ($p > .05$) among groups.

CHAPTER V

Discussion, Conclusions, Implications, Recommendations and Summary

Chapter V is organized into 5 sections: (1) Discussion, (2) Conclusions, (3) Implications, (4) Recommendations (5) Summary. The discussion will review the hypotheses in the context of the theoretical framework. The conclusions were drawn from interpretation of the data. Also, this chapter will review implications to related nursing practice and any recommendations for further research.

Discussion

The purpose of this research was to provide answers to two questions: (1) was the combination of propofol plus ketamine delivered as a low dose perioperative infusion more efficacious than propofol alone on postoperative pain perception in laparoscopic surgical patients and (2) was a low dose perioperative infusion of propofol plus ketamine more efficacious in males compared to females?

The study design was a double-blind, 2 X 2 factorial design. The sample used was a convenience sample of competent adult male and female laparoscopic surgery patients classified by the American Society of Anesthesiologists Physical Status categories of I through III between the ages of 18 to 65 who gave informed consent. The sample size was determined using a medium effect size of 0.35, alpha of 0.05, and power (1-β) of 0.80. The formula here was suggested by (Cohen, 1998) for 2 X 2 factorial studies to determine the number per cell. The required sample size was 68. Using 20% for attrition, or sample size was adjusted to 84. There were 57 participants with 37 females and 20 males. Due to attrition, there were two males lost from the study.

The theoretical framework was the Gate Control Theory which was based on the work of Melzack and Wall (1965). The theory focused on A-β and C type afferent pain fibers, the structure and function of the proposed "gate" in the dorsal horn, and physiologic pain modulation mechanisms that descend from the brain or are constitutive in the dorsal horn. There is evidence (Woolf, 1983; Woolf & Thompson, 1991) pointing

toward central sensitization, a state of hypersensitivity to noxious and non-noxious stimuli following a painful event such as surgery, which provides an important explanation of dorsal horn plasticity not completely described in the Gate Control Theory. Therefore, the Gate Control Theory was presented together with peripheral and central sensitization as the theoretical framework for this study (see figure 1).

Within the framework of the Gate Control Theory, afferent impulses, such as those evoked from surgical tissue trauma, are transmitted to three functional spinal cord systems. Peripheral pain impulses enter the dorsal horn and synapse in the substantia gelatinosa, the first of the three spinal cord systems. The second system includes those fibers that ascend rhostrally to the brain in the dorsal columns. The third system involves central transmission cells that receive modified impulses from the substantia gelatinosa, where the gate control system is located (Melzack & Wall, 1965).

Melzack and Wall (1965) describe the substantia gelatinosa as a functional unit, which spans the spinal cord and consists of densely packed cells. These cells interrelate by short fiber synapses and longer fibers from Lissauer's tract. The substantia gelatinosa is considered a gating site where small and large fiber afferent signals are modulated.

The modulation from higher centers exhibits sex differences. Estrogen receptors have a widespread distribution throughout the central nervous system with a sex-dependent dimorphic expression. Dimorphic receptors are also co-located with receptors responsible for pain and may explain why male and female subjects report different levels of pain following a nociceptive event. Menstrual cyclicity has been suggested to influence the pain experience and response. Given the hormonal changes associated with the menstrual cycle and concomitant affective fluctuation, nociceptive events may or may not be interpreted as painful (Berkley, 1997).

Peripheral sensitization, a *post facto* consequence of tissue damage and chemical mediators released during an inflammatory response, alters transduction in nociceptors that normally have relatively high thresholds. Substance P and calcitonin gene related

peptide (CGRP) are neuroactive substances that act on inflammatory cells, endothelial cells, and smooth muscle to produce vasodilatation and cellular leakage into the interstitial milieu surrounding A-β, Alpha-δ, and C fibers. Bradykinins, cytokines, histamine, hydrogen ions, leukotrienes, nerve growth factor, norepinephrine, neuropeptides, potassium ions, prostaglandins, and serotonin (5-HT) are synergistically active at afferent terminals where these chemicals increase nociceptive transduction producing peripheral sensitization (Woolf & Chong, 1993). Peripheral sensitization is fundamentally different from central sensitization. It is characterized by the conversion of the Alpha-β fiber, a high threshold fiber that normally signals innocuous events, into a low threshold nociceptive transducer (Woolf, 1991; Woolf & Chong, 1993).

Central sensitization is characterized by three changes within the dorsal horn: 1) reduced threshold of dorsal horn neurons in the substantia gelatinosa, 2) increased responsiveness to both noxious and benign stimuli, and 3) subsequent expansion of the receptive fields. Receptive fields of dorsal horn neurons, described by Woolf & Chong (1993) are constituted by an area subdivided into two zones called the firing zone and the subliminal zone. The firing zone, generally the center of the receptive field, is the location of afferents that trigger action potentials in the dorsal horn neurons with an adequate stimulus. The subliminal zone circumferentially surrounds the firing zone and the afferent fibers originating here normally do not trigger an action potential in the dorsal horn. However, dorsal horn cells are in a prolonged depolarized state following the establishment of central sensitization and are easily brought to threshold by subliminal zone afferent fibers that normally carry subthreshold signals. Stubhaug (1997) describes an area of punctate mechanical hyperalgesia or tactile allodynia which surrounded the surgical wounds of the participants in his study. The area of hypersensitivity appears to include the firing and subliminal zones described by Woolf & Chong (1993) and was significantly larger in the placebo group suggesting the establishment of central sensitization, which will be discussed in detail next.

The initial step of sensitization in the dorsal horn includes Alpha-δ and C fibers generating slow synaptic potentials through release of glutamate, an amino acid transmitter, and two excitatory neuropeptides, substance P and neurokinin A. Glutamate acts on AMPA receptors, increasing the conductance of sodium through its ion channel. NMDA receptor ion channels are functionally blocked by magnesium. The magnesium block is reversed as sodium conductance through AMPA receptors depolarizes the cell. Calcium and sodium currents through NMDA receptors result in a long-lasting depolarization in the post-synaptic cell (Woolf, 1983; Woolf & Chong, 1993).

Calcium influx increases second messenger concentrations that activate protein kinase phosphorylation of membrane proteins, such as ion channels and the NK-1 and NK-2 receptors (Woolf & Chong, 1993). Prolonged excitatory post-synaptic potentials arriving from the expanded receptive field (following surgery) cause progressive depolarization. Subsequent afferent stimuli that previously would not have exceeded threshold trigger action potentials in the dorsal horn neurons which carries the pain signal rhostrally for interpretation. The NMDA receptor is largely responsible for the initial central sensitivity, maintenance of a reduced threshold, and hyperalgesia seen in acute pain states. Studies have demonstrated that administering an NMDA antagonist prevents the establishment of central sensitization (Coderre & Melzack, 1992; Stubhaug, 1997; Woolf & Chong, 1993).

The NMDA receptor ion channel is blocked by magnesium and activation follows ligand binding and voltage-dependent reversal of the magnesium blockade. The voltage-dependent NMDA activation follows glutamate binding to the AMPA receptor causing its ion channel to open and sodium to enter the cell. The membrane potential reverses sufficiently to activate both voltage-gated calcium and NMDA receptor ion channels. The magnesium blocking the NMDA ion channel is removed, permitting the entry of calcium and sodium, with potassium efflux (Andersen et al., 1996; Coderre & Melzack, 1992; Woolf & Chong, 1993).

Following activation of the NMDA receptor, the intracellular concentration of calcium increases which activates a second messenger systems. Persistent NMDA activation, as in the post-surgical patient, leads to phosphorylation of membrane bound proteins and ion channels. Phosphorylation results in a membrane that has increasingly permeable with a persistent reduction in threshold. Central sensitization does not occur without the activation of the NMDA receptor (Wilder-Smith, 2000; Woolf & Thompson, 1991).

NMDA receptor antagonism has been demonstrated to prevent establishment of central sensitization from the increased afferent transmission secondary to surgical tissue damage. Research investigating the NMDA antagonist, ketamine, describe outcomes where opioids clearly failed to prevent central sensitization, suggesting that the NMDA receptor initiates and maintains central sensitization (Stubhaug, 1997; Woolf & Chong, 1993). Conversely, the use of ketamine, a NMDA receptor antagonist, should inhibit central sensitization and result in a study patient having a longer Time to First Request (TTFR), a lower 24 hour total morphine equivalent use, and lower VAS pain scores.

Interestingly, our findings with respect to TTFR exposed a paradoxical trend which may be explained by current research. Specifically, the trend observed was that males who received ketamine requested postoperative analgesics one hour earlier than males in the saline group. It is important to note that TTFR represents the short term effect of ketamine. This trend may represent an increased perception of pain when compared to the saline group. Although this trend was not statistically significant ($p > .05$), it does not contradict earlier studies on the topic.

A study by Fu et al. (1997) suggested that ketamine administered at low doses (.5mg/kg) appear to have a greater affinity for the NMDA receptor. However, ketamine has an affinity for multiple receptor sites which include various glutamate receptors. Inhibition of glutamate receptors lead to changes within the cortical regions of the brain. The administration of ketamine results in an increase of glutamate in the cortex with the

greatest increases in glutamate associated with subanesthetic doses (Liu & Moghaddam, 1995; Moghaddam, Adams, Verma, & Daly, 1997). Further, ketamine may also increase cortical concentrations of dopamine (Marino & Conn, 2002; Sershen, Hashim, & Lajtha, 1998).

With blockade of NMDA receptors throughout the brain, dopamine levels increase and excite the thalamus. When the thalamus exists in an excited state, the result is a large increase in cortical glutamate release. These increases in glutamate, dopamine, and other monoamines secondary to administration of ketamine may be the trigger resulting in altered sensory perception and could influence a person's perception of pain. This is described as anhedonia or the inability to feel well (Ereshefsky & Miller, 2002). The effect of anhedonia may have skewed data from the VAS and the TTFR. We may have been measuring anhedonia rather than pain. This process may explain why males who received ketamine requested postoperative analgesics one hour earlier than males in the saline group.

Our findings with respect to 24 hour morphine equivalent use revealed a trend that is not only intuitive but does not contradict earlier studies of ketamine's efficacy as an analgesic (Andersen et al., 1996; Fu et al., 1997; Roytblat et al., 1993). In contrast to TTFR representing the short term effect of ketamine, the 24 hour morphine equivalent use represents the long term effect of ketamine. Although no statistically significant findings ($p > .05$) were demonstrated through our data analysis; again, a clear trend that does not contradict current research is apparent. Specifically, both males and females who received ketamine had lower 24-hour total morphine equivalent use when compared to the saline groups.

There were no trends or significant findings ($p > .05$) noted with regard to VAS scores as a function of interval measurements. The measurement intervals were:

Interval I was the TTFR of analgesics.

Interval II was 30 min after arrival in the PACU.

Interval III was at the time of discharge from PACU.

Interval IV was 24 hours after termination of the perioperative infusion.

When 24-hour morphine equivalent use as a function of hormonal milieu was analyzed, no statistically significant findings ($p > .05$) were observed. However, the trend we found was females in the luteal phase had lower 24 hour morphine use in both experimental and control groups when compared to other groups. Much of the research on the impact of temporal hormonal characteristics on nonreproductive functions has focused on menstrual cyclicity. Estrogen peaks about one week after ovulation and is opposed by a progesterone peak. Estrogen remains unopposed during the follicular phase, while later during the luteal phase, progesterone opposes the effects of estrogen (Badwe, Mittra, & Havaldar, 1999).

When the experimental data was explored with regard to TTFR as a function of hormonal milieu, we found that females in the luteal phase who received ketamine had a significantly ($p < .05$) longer time to first request than females in the follicular phase. This finding is consistent with the trend previously described concerning total morphine equivalent use as a function of hormonal milieu.

Due to the limited volume of research in both animal and human models, the literature is not conclusive with respect to the efficacy of analgesics as a function of hormonal milieu. Some research suggests that pain tolerance is improved during the luteal phase (Bartok & Craft, 1997). Other research suggests that kappa opioids produced significantly greater analgesia in women than men (Gear, Gordon et al., 1996; Gear, Miaskowski et al., 1996). In contrast, another study demonstrated no significant male-female differences or estrous cycle-related changes in the level of kappa opiate induced analgesia (Kavaliers & Choleris, 1997). The contradictory nature of results in the literature point to the need for further research in sex differences.

Conclusions

The purpose of this research was to provide answers to two questions: (1) was the combination of propofol plus ketamine delivered as a low dose perioperative infusion more efficacious than propofol alone on postoperative pain perception in laparoscopic surgical patients and (2) was a low dose perioperative infusion of propofol plus ketamine more efficacious in males compared to females?

Analysis of the data revealed trends that were both expected and unexpected. Specifically, males who received ketamine requested postoperative analgesics one hour earlier than males in the saline group which was unexpected. This may be explained by the influence of gender-specific kappa opioid, monoamine, and glutamatergic responses.

The second trend observed was expected, in that the total 24 hour morphine equivalent use was less in the experimental groups when compared to the control groups. Although both of these trends were not statistically significant, they do not contradict earlier studies.

The third trend showed females in the luteal phase had lower 24 hour morphine use in both experimental and control groups when compared to other groups. The literature is not conclusive with respect to the efficacy of analgesics as a function of hormonal milieu. Some research suggests that pain tolerance is improved during the luteal phase while other research suggests the contrary.

Last, when experimental data was explored with regard to TTFR as a function of hormonal milieu, we found that females in the luteal phase who received ketamine had a significantly ($p < .05$) longer time to first request than females in the follicular phase. This finding is consistent with the trend previously described concerning total morphine equivalent use as a function of hormonal milieu.

Strengths and Weaknesses

The strengths of this study included:

1. The study was a double blind, placebo controlled clinical trial.

2. Gender was blocked by randomly assigning males and females separately to either the experimental or control group.
3. The study was approved by two independent review boards.
4. The measurement of pain was triangulated using TTFR, 24 hour morphine equivalent use, and VAS scores.
5. Our data had a normal distribution and did not demonstrate a statistically significant difference among or between groups.

The weaknesses of this study included:

1. For external reasons, namely, deployments due to war, we failed to reach our sample size. The intimate relationship between sample size and power increased our potential for Type II error. Meaning, significance could exist without our ability to detect it.
2. Our ketamine dose of 3.125 mcg/kg/min may have been too small to allow detection of a significant treatment effect.
3. Self reporting of menstrual cycle may have led to incorrectly categorizing females data based on the hormonal milieu.
4. VAS intervals 1 and 3 not being temporally standardized may have skewed data for our repeated measures analysis.
5. The VAS is used to measure a number of perceptions; 2 examples being pain & satisfaction. It is a possible we measured anhedonia rather than pain.
6. Variable postoperative pain medication regimens existed and morphine equivalent use was calculated (Appendix G).
7. VAS data was collected by PACU staff whose primary role was caring for their patients during phase I recovery.

Implications

If the previously discussed trends continue in future research, it may be demonstrated that ketamine is more efficacious in females compared to males. Our research showed only one significant difference with respect to our dependent variables; therefore, we do not recommend any change in anesthesia practice with regard to ketamine at this time.

Recommendations

Concerning our research, we recommend the following:

1. Continue data collection until the sample size requirements are met.
2. Increase the low-dose perioperative ketamine from 3.125 mcg/kg/min to 6 mcg/kg/min to increase ketamine's action at the kappa opioid receptor
3. To use a dopaminergic antagonist to attenuate the phenomenon of increased dopamine; which may decrease anhedonia and increase reliability of the VAS.
4. The results of our study and previous studies are attributed to the kappa receptor activity, the NMDA receptor antagonism, or both. The use of selective agents would allow the investigator to logically discern the cause and effect relationship.
5. Laboratory analysis of female plasma hormonal levels would eliminate the potential for self-reporting error and incorrect categorizing of menstrual phase.

Summary

Three trends found were not statistically significant but do not contradict findings in current literature:

1. Males who received ketamine requested postoperative analgesics 1 hour earlier than males in the saline group.

2. Males and females who received ketamine had lower 24-hour total morphine use.
3. Females in the luteal phase had lower 24 hour morphine use in both experimental and control groups when compared to other groups.

The one trend found that demonstrated statistical significance was TTFR as a function of hormonal milieu, which showed that females who received ketamine and were in the luteal phase had statistically significant longer TTFR.

The findings from this study are important for several reasons. Current perioperative analgesic regimens often include opioids and other analgesics that fail to effectively prevent establishment of central sensitization. For millions of patients who undergo surgery annually, the administration of low doses of ketamine may reduce pain to levels unobtainable with opioids alone due to toxicities. The identification of activated NMDA receptors as an essential component in the establishment of central sensitization illuminates a role for ketamine, a non-competitive NMDA antagonist. Reduction in pain is important to reduce the negative physiological sequelae of poorly managed pain and can decrease length of stay for patients. Sex differences were considered in this study as a growing body of evidence points to hormonal and gender-related influences on pain perception.

APPENDIX A

Consent Form

Consent Form

VOLUNTEER AGREEMENT AFFIDAVIT

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

Authority:	10 USC 3013, 44 USC 3101, and 10 USC 1071-1087.
Principal Purpose:	To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and location purposes.
Routing Uses:	The SSN and home address will be used for identification and location purposes. Information derived from the study will be used to document the study, implement medical programs, adjudicate claims, and for the mandatory reporting of medical conditions, as required by law. Information may be furnished to Federal, State, and local agencies.
Disclosure:	The furnishing of your 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(1)-VOLUNTEER AFFIDAVIT

Volunteers Subjects in Approved Department of the Army Research Study

Volunteers under the provisions of AR 40-38 and AR 40-25 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 attain my _____ birthday, do hereby volunteer/give consent as legal

representative for _____ to participate in **a study titled "Effects of Perioperative Low Dose Ketamine Infusion on Postoperative Pain Perception in Males and Females Undergoing Laparoscopic Surgery."**

under the direction of **CPT Warren Cusick**

conducted at **William Beaumont Army Medical Center**

The implications of my voluntary participation as legal representative; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconvenience 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 or the rights of the person I represent on study-related injury, I may contact **The Staff Judge Advocate**

at **Bldg 113, Fort Bliss, Texas 79916 (915) 568-7141**

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

PART A (2) - ASSENT VOLUNTEER AFFIDAVIT *(MINOR CHILD)*

I, _____, SSN _____ having full

capacity to assent and having attained my _____ birthday, do hereby volunteer for _____

(Research Study)

under the direction of _____

conducted at _____

(Name of Institution)

WILLIAM BEAUMONT AMC
PROTOCOL # 02130
IRB APPROVAL 20 Aug 02
APPROVAL EXPIRES 31 Oct 2003

(Continued on Reverse)

PART A (2) - ASSENT VOLUNTEER AFFIDAVIT

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 inconvenience 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 I may contact:

_____

at _____

(Name, Address, and Phone Number of Hospital (Include Area Code))

I understand that I may at any time during the course f this study revoke my assent and withdraw from the study without further penalty or loss of benefits; however, I may be requested to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for 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 - TO BE COMPLETED BY INVESTIGATOR

INSTRUCTIONS FOR ELEMENTS OF INFORMED CONSENT: *(Provide a detailed explanation in accordance with appendix C, AR 40-38 or AR 70-25.)*

PARTICIPATION INFORMATION: You have been invited to participate in a clinical investigation/research study conducted at William Beaumont Army Medical Center. It is very important that you read and understand the following general principles that apply to all participants in our studies: (a) Your participation is entirely voluntary; (b) You may withdraw from participation in this study or any part of the study at any time; refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled; (c) After you read the explanation, please feel free to ask any questions that will allow you to clearly understand the nature of the study..

PURPOSE: To determine the effects of low dose intravenous (into the vein) infusion of ketamine on postoperative (after surgery) pain perception in males and females undergoing laparoscopic surgery. A similar study conducted by Roytblat, L., Korotkoruchko, A., Katz, J., Glazer, M., Greemberg, L., & Fisher, A. in 1993, twenty female participants who underwent gall bladder removal surgery demonstrated that ketamine reduced postoperative pain scores, increased the pain free period from the end of surgery until the participants needed pain medicine, and reduced the total amount of pain medicine needed by the participants that received ketamine.

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

SIGNATURE OF VOLUNTEER	DATE	SIGNATURE OF LEGAL, GUARDIAN, (*If volunteer is a minor)*
PERMANENT ADDRESS OF VOLUNTEER	TYPED NAME OF WITNESS	
	SIGNATURE OF WITNESS	DATE

REVERSE OF DA FORM 5303-R, MAY 89

VOLUNTEER AGREEMENT AFFIDAVIT (DA 5303-R, Part B, Continued) - Revised 14 Feb 03 (per CIRO recommendations); Amended 21 Jul 03 (extension of completion date)
STUDY TITLE: Effects Of Perioperative Low Dose Ketamine Infusion on Postoperative Pain Perception in Males and Females Undergoing Laparoscopic Surgery.

DURATION OF STUDY: Start: September 2002 Est Complete: October 2003

EXPECTED DURATION OF SUBJECT'S PARTICIPATION: If you decide to participate, the study will begin when you enter the operating room. Ketamine will be started just before your surgery begins and the study will end 24 hours later. If you volunteer to participate in the study you will have to complete a pain score tool and short questionnaire. The questionnaire contains information pertaining to the name and total amount of the drug you used for postoperative pain management. The pain score tool and short questionnaire will be sent home along with an stamped envelope addressed to the principal investigator. The pain score tool and short questionnaire are very important to determine the effects of ketamine. We ask that you return the completed pain score tool and short questionnaire by mail within 3 days. Neither your operation nor your hospital stay will be prolonged.

PROCEDURES TO BE FOLLOWED: Participants will be given an opportunity to enroll in this study if they are undergoing laparoscopic surgery in either the General Surgery or Gynecological Surgery services. Ketamine will be placed in an intravenous (IV) solution of Propofol. Propofol is one of the most commonly administered drugs by anesthesia providers during surgery.

This is a randomized (by chance), placebo controlled (dummy drug), double blind study. Double blind means that neither you nor your study doctor will know to which treatment group you are assigned; however, that information is available if it is necessary. The randomization process is like flipping a coin and you will have one in two chances to be assigned to one of the two groups. One group will receive the propofol and ketamine in combination (which is the standard of care) and another group will receive propofol and saline (dummy drug). The second group will be receiving the investigational treatment, as specified above. During the surgery, both groups will receive fentanyl, a strong pain medicine.

On the day of surgery, the participant will be brought to the operating room, moved to the operating room bed, and receive a general anesthetic through an IV. The infusion of propofol and ketamine or propofol and placebo will be started immediately after you go to sleep and will be discontinued 15 minutes before the end of the surgery. Once the surgery is over, you will be asked to score your pain using a pain scale at 4 different times. They are at 30 minutes after arrival in the recovery room, the time you first request pain medicine, upon discharge from the recovery room, and at the 24 hour mark following the discontinuation of the drug infusion. If you go home prior to this described 24 hour pain scoring time, we ask that the pain score tool and the short questionnaire be returned in the stamped envelope within 3 days. At the 24 hour mark, participation in this study is ended.

REASONABLY FORESEEABLE RISKS OR DISCOMFORTS: The risks associated with ketamine administration are: dizziness, blurred vision, distorted body image, hallucinations, nausea, vomiting, and hypersalivation. There is an additional risk of vivid dreams. However, these risks are usually associated with higher doses (more than 2 mg/kg or higher) of ketamine In addition, the incidence of these side effects is reduced when intravenous benzodiazepines are

VOLUNTEER AGREEMENT AFFIDAVIT (DA 5303-R, Part B, Continued) - Revised 14 Feb 03 (per CIRO recommendations); Amended 21 Jul 03 (extension of completion date)
STUDY TITLE: Effects Of Perioperative Low Dose Ketamine Infusion on Postoperative Pain Perception in Males and Females Undergoing Laparoscopic Surgery.

administered prior to ketamine, which is part of the protocol of this study. The risk is minimal that you will experience an allergic reaction to ketamine or propofol. Only 1 occurrence of an allergic reaction to ketamine has been reported in the literature since the 1980s.

UNFORSEEABLE RISKS: There are circumstances that may pose unforeseeable risks by participation in this study; however, all procedures will be conducted in a safe manner considering currently understood anesthesia practice.

BENEFITS TO THE SUBJECT OR TO OTHERS: There may be no direct benefits to you for participating in this study. However, participants who receive ketamine may have reduced pain following surgery and require less pain medicine to control pain. Propofol is a sedative medication. Propofol may also decrease the occurrence of nausea and vomiting in the immediate period following surgery.

ALTERNATIVE PROCEDURES OR COURSES OF TREATMENT: Your participation in this study is completely voluntary. You may withdraw at any time without any consequences. Alternative anesthetics are available which follow set standards of care. Various forms of anesthesia can be discussed with an anesthesia provider during the preoperative anesthetic patient interview.

APPROXIMATE NUMBER OF SUBJECTS INVOLVED IN THE STUDY: 84.

ASSURANCE OF CONFIDENTIALITY: During the course of your treatment as a patient at William Beaumont Army Medical Center, you have been provided a copy of the Privacy Act Statement (DD Form 2005), which has made you aware of the safeguards available because of the Privacy Act of 1974 and the Health Insurance Portability and Accountability Act (HIPAA) of 1996. You have been given the opportunity to review the DD Form 2005, ask questions, and retain a personal copy. Information gained because of your participation in this study may be publicized in the medical literature, discussed as an educational model, and used generally in the furtherance of medical science. Information gained from this study may be used as part of a scientific publication in medical or professional journals, but you will in no way be personally identified. The William Beaumont Army Medical Center Institutional Review Board (IRB) and other governmental agencies may review your records, as part of their normal duties. Complete confidentiality cannot be promised, particularly to subjects who are military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities.

SIGNIFICANT NEW FINDINGS: Your physician will notify you of any significant new findings developed during the course of this study that might have a bearing on your willingness to continue your participation.

VOLUNTEER AGREEMENT AFFIDAVIT (DA 5303-R, Part B, Continued) - Revised 14 Feb 03 (per CIRO recommendations); Amended 21 Jul 03 (extension of completion date)
STUDY TITLE: Effects Of Perioperative Low Dose Ketamine Infusion on Postoperative Pain Perception in Males and Females Undergoing Laparoscopic Surgery.

STUDY RESULTS: Results of this study will be made available to you upon request. Please note that the study is scheduled to be completed on or about October 2003. It is the intention of the investigators to publish the results in professional anesthesia journals. Participants will never be identified in any publication.

ADDITIONAL COSTS/PAYMENTS TO SUBJECT THAT MAY RESULT FROM PARTICIPATION IN THIS STUDY: Daily charges to study participants will be waived per AR 40-38, paragraph 3-3j(2). You will not receive any compensation (payment) for participating in this study.

STATEMENT OF GOOD FAITH: There is no guarantee or promise that you will receive benefits from this study; however, you understand that the principal investigator, CPT Warren Cusick, SRNA, will undertake his best efforts to keep you informed of any serious complications which may result from your participation in this study.

DOMICILIARY STATEMENT/ENTITLEMENT TO CARE: In the event of physical injury resulting from the investigational procedures, the extent of medical care provided, should it become necessary, is limited and will be within the scope authorized for DOD health care beneficiaries IAW AR 40-38, paragraph 3-3j. Necessary medical care does not include domiciliary (home) care or nursing home care. Federal laws and regulations govern your entitlement to medical and dental care and/or compensation in the event of injury. Because you are a military beneficiary, participation in this study does not alter your ongoing medical benefits as a military beneficiary (except as noted under "Reasonably Foreseeable Risks or Discomforts") and you will continue to receive any necessary medical treatment should you experience illness or injury as a result of this study.

INFORMED CONSENT FOR FEMALE RESEARCH VOLUNTEERS WHEN ABSENCE OF PREGNANCY IS REQUIRED DURING THE COURSE OF A CLINICAL INVESTIGATION PROJECT: During the course of this study, absence of pregnancy is required. The medications/procedures involved in this study may have significant risk to the fetus or you, if pregnant. Therefore, you agree not to participate in this study if you believe that you are pregnant and you agree to prevent pregnancy during the course of this study. If there is a possibility of pregnancy (a late period and/or sexual activity without birth control), you agree to request testing and evaluation to diagnose pregnancy before participating in this study. This request, testing and evaluation will be handled with guarantees of privacy and confidentiality, and the results will be made available only to you and/or your doctor. If pregnant, you agree to withdraw from this study and seek medical attention.

SAGEGUARDS TAKEN: The drugs used are sterile and will be injected in a way to minimize any problems associated with intravenous (into the vein) administration. Your physician will notify you of any significant new information about ketamine, which develops during your treatment that may relate to your willingness to continue in this study

VOLUNTEER AGREEMENT AFFIDAVIT (DA 5303-R, Part B, Continued) - Revised 14 Feb 03 (per CIRO recommendations); Amended 21 Jul 03 (extension of completion date)
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This study has undergone review by the Institutional Review Board at William Beaumont Army Medical Center and the Committee for the Protection of Human Subjects at the University of Texas Health Science Center-Houston to ensure this study meets the most current established safety and ethical standards governing the conduct of research.

CONSEQUENCES OF SUBJECT'S DECISION TO WITHDRAW FROM THE STUDY: There are no consequences to you if you withdraw from the study. You may withdraw at any time.

CIRCUMSTANCES UNDER WHICH YOUR PARTICIPATION MAY BE TERMINATED WITHOUT YOUR CONSENT:

(a) Health conditions under which your participation possibly would be dangerous:

- History of Hepatitis
- Bleeding Disorders
- Allergy to Ketamine
- Chronic or acute liver disease
- History of major or severe affective and/or anxiety disorder
- History of Human Immunodeficiency Virus (HIV) infection
- Patients with cancer

(b) Other conditions, which might occur that, make your participation detrimental to you or your health: Pregnancy

FOR FURTHER INFORMATION, please contact the principal investigator, CPT Warren Cusick, SRNA at the Dept. of Anesthesia, WBAMC, (915) 569-1970/1920.

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE PRINCIPAL INVESTIGATOR, CPT WARREN CUSICK, OR THE ASSOCIATE INVESTIGATOR, CPT JEFFREY CONROY, BEFORE SIGNING.

PLEASE CHECK ONE OF THE FOLLOWING:

I do _____ do not _____ agree to allow a copy of this form to be placed in my medical records.

_____ Volunteer's (or legal guardian's) initials

YOU WILL BE PROVIDED A COPY OF THIS FORM TO TAKE WITH YOU: Before giving your consent by signing this form, you have had an opportunity to ask questions about study procedures and study medications, their conveniences, hazards, and side effect. Based on

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this information, you can voluntarily agree to participate in this study. All oral information and discussions about the study are in a language that you understand. You can continue to ask and have questions answered during the study. You agree that you have read this consent and that you have received a copy of it.

Having thoroughly read, understood, and having had a full explanation of the above information, your signature below shows that you voluntarily choose to participate in this study. You may withdraw from the study at any time after signing this form, without jeopardizing present or future care, should you wish to do so. By signing this form, you have not waived any of the legal rights that you otherwise would have as a participant in a research study. If you elect to sign this consent form, you will receive a signed and dated copy of this form.

_____	_____	_____
Printed Name (Volunteer or legal guardian if volunteer is a minor)	Signature	Date

_____			
Permanent Address	City	State	Zip

_____	_____	_____
Printed Name of Person Consenting (must be associated with the study)	Signature	Date

_____	_____	_____
Printed Name of Witness (authentication of the consent process)	Signature	Date

HIPAA RESEARCH AUTHORIZATION

WBAMC Protocol #02/30, Effects of Preoperative Low Dose Ketamine Infusion on Postoperative Pain Perception in Male and Females Undergoing Laparoscopic Surgery

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Authorization for the Disclosure and Use of Your Health Information (Amended 21 July 2003)

By signing this authorization form, you are authorizing William Beaumont Army Medical Center, including the Principal Investigator, CPT Warren T. Cusick, and other members of the research staff, to use and disclose your health information to determine the effects of low dose intravenous (into the vein) infusion of ketamine on postoperative (after surgery) pain perception in males and females undergoing laparoscopic surgery. This health information includes demographic information (i.e. age, sex, race, etc.), medical/surgical history, imaging studies, laboratory results, and any other health information relating to this research study.

Your health information may be disclosed to Institutional Review Boards that review this research to make sure that it is ethical; and state and federal government agencies, including, but not limited to, the Food and Drug Administration (FDA), the Department of Health and Human Services, and Department of Defense regulatory agencies. Health information that has been disclosed may be re-disclosed by the recipient of the information.

This authorization expires in October 2003 or upon final publication of the results of the research, whichever comes later.

You have the right to revoke this authorization in writing, unless William Beaumont Army Medical Center has already taken action relying on this authorization. You may revoke this authorization by writing to the Principal Investigator at Anesthesia Nursing, WBAMC, 5005 N. Piedras Street, El Paso, TX 79920.

Any medical treatment that is to be provided as part of this research study will be provided only if you authorize the uses and disclosures of your health information as described.

Since this is a blinded study, William Beaumont Army Medical Center will not disclose your health information to you during the course of the research study. You may request copies of records containing your health information after the research is completed."

If you have not already received a copy of the Military Health System Notice of Privacy Practices, you may request one. If you have any questions or concerns about your privacy rights, you should contact Mr. Jack Bell, Patient Administration Division, at (915) 569-2198.

HIPAA RESEARCH AUTHORIZATION (cont), WBAMC Protocol #02/30, Effects of Preoperative Low Dose Ketamine Infusion on Postoperative Pain Perception in Male and Females Undergoing Laparoscopic Surgery

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You will receive a copy of this form after it is signed.

_____ _____

Volunteer's signature or Personal Representative Date

_____

Volunteer's Printed Name or Personal Representative

APPENDIX B

Research Protocol

Research Protocol

Premedication:	Versed 1-3mg IV
	Fentanyl 100-250mcg IV prior to induction
	No Lidocaine
Induction:	Propofol 1-2mg/kg
	Rocuronium 0.5-0.7mg/kg
	Intubate/Secure ETT
	Turn on Study Infusion on Alaris Pump
	Select option button/enter new program/page to and select "Drug?"
	Dose at 12.5mcg/kg/min; please record start and stop times in notes, document in gtt in IV section
Maintenance:	Isoflurane/O2/N2O (use 50:50 mix of O2:N2O)
	Fentanyl 3-6mcg/kg/hr
	(1^{st} hour fentanyl includes preinduction fentanyl)
	Rocuronium titrated to TOF response
Antiemetic:	Zofran 4mg IV 30 minutes out
	Turn off study infusion 15 minutes out
	May increase N20 at end of case
Reversal:	Neostigmine 0.07mg/kg
	Robinul 0.01mg/kg
PACU orders:	No Demerol, No Fentanyl, No Ketorolac
	Circle MSO4 and Zofran only

APPENDIX C

Demographic Data Sheet

Demographic Data Sheet

1. Sex:_____
2. Age on last birthday:_____
3. Height:_____
4. Weight:_____
5. Date of last menstrual period:_____
6. Oral contraceptive or hormonal replacement therapy use:_____
7. Surgical procedure:_____
8. ASA category:_____
9. Surgeon:_____

Participant #_____

APPENDIX D

Data Collection Sheet

Data Collection Sheet

Total amount of local anesthetic used intraoperatively _____cc _____%

Total opioid use for 24 hours

Medication	Dose	Time	Amount administered	Route of administration

Time to first request of pain medicine

Infusion Time Off _____ **Time 1st Request** _____ **Total min**_____

Number of ketamine related side effects for 24 hours

Dizziness	Blurred vision	Hallucinations	Distortions in body image	Nausea	Vomiting	Hypersalivation

Participant #_____

APPENDIX E

Visual Analog Scale

Visual Analog Scale

No Pain  Worst Possible Pain

☐ 30 min ☐ 1st Request ☐ D/C from PACU

Participant #_____

APPENDIX F

VAS Instruction Protocol

VAS Instruction Protocol

This protocol was developed to limit error when study participants complete the 100 mm Visual Analogue Scale (VAS) at four separate times. The protocol is designed to ensure that each participant receives identical VAS completion instruction.

1. Participants will be shown the actual 100 mm VAS on the day they are given the opportunity to participate in this study.

2. The Principle and/or Associate Investigator(s) introduce participants to the horizontally oriented 100 mm VAS. PACU or Ward nurses may reinforce steps 3 - 14.

3. Point out that the instrument is to score their pain.

4. Point out the vertical stops and state that these are the limits of the line and that marks made outside these limits cannot be scored.

5. Point out the verbal descriptor "no pain" outside the left vertical limit.

6. Point out the verbal descriptor "worst possible pain" outside the right vertical limit.

7. Tell the participant that they should make a straight vertical line at a 90° angle across the horizontal line with a pen that most closely matches the level of pain that they are immediately experiencing. The nurse will provide a pen to the patient.

8. Make no reference to what any point along the line could mean. For example, do not tell the patient that any mark above a certain point will be an indicator that they need pain medicine.

9. During the initial instruction, the participant should complete one VAS to demonstrate that they understand how to use the instrument.

10. Tell the patient that on the day of surgery they will be asked to complete three VAS instruments to score their pain, most likely in the Post Anesthesia Care Unit (PACU).

11. Tell the patient if they are still in the hospital they will be asked to complete a VAS at 24 hours following the time that the investigational drug was turned off.

12. Tell the patient that they will be given a VAS to take home with them with the time that they should record their pain identical to how they did following their surgery.

13. Emphasize the importance that participants return the mail-in 100 mm VAS using the pre-addressed stamped envelope at their first possible convenience.

14. Tell participants the study investigators will call them once in the first 3 days to remind them to complete and return the VAS.

VAS Instruction Protocol

15. Investigators score the VAS to the nearest 2 mm with the 100 mm overlay grid. Write this score above the VAS.

16. Use a pen to check the box below the VAS instrument that corresponds to either: (a) 30 minutes postoperative, (b) time to first analgesic request, or (c) PACU discharge.

17. Realize the time to first analgesic request may not occur in the PACU. This fact should be communicated by the PACU nurse to the ward nurse accepting care for the study participant and the VAS instrument delivered to the ward with the chart for recording on the ward. The ward nurse should be told that the patient is a participant in a research study and requires collection of one more data point with the VAS.

18. This protocol is to be given as instruction by either the principle or associate investigator(s) to PACU and ward nurses and included in the participant research folder that is kept with the chart.

APPENDIX G

Morphine Equivalent Dose

Morphine Equivalent Dose

Drugs calculated to 10 mg parental morphine sulfate

Drug	Dose	Morphine equivalent
Acetaminophen/codeine	1 tablet	1.5 mg
Acetaminophen/oxycodone	1 tablet	1.67 mg
Fentanyl	100 mcg	10 mg
Hydromorphone	1 mg	6.66 mg
Ketorolac	30 mg	9 mg
Tramodol	100 mg	10 mg

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VITA

Jeffrey Patrick Conroy was born at the Portsmouth Naval Shipyard in Kittery, Maine, on September 19, 1967; the son of Fredrick John Conroy and Margaret Juliet Moeykens. He enlisted in the United States Army in 1984. He left active duty and entered Eastern Kentucky University on a full scholarship from the Reserve Officer Training Corps (ROTC) program. By graduation in 1996, he had earned a Baccalaureate of Science Degree in Nursing with honors, a minor in Military Science, Distinguished Military Graduate standing in his ROTC program, induction into Sigma Theta Tau Honor Society of Nursing, and membership in the Golden Key Honor Society. He earned a Regular Army commission in 1996 and has served as a critical care nurse at the United States Military Academy at West Point, NY and Fort Hood, Texas. He entered the United States Army Graduate Program in Anesthesia Nursing in 2001. In 1992, he married Annette Carrión Laureano of Luquillo, Puerto Rico. They have three daughters, Mercedes, Isabella, and Elena.

VITA

Warren Turley Cusick, was born in Rosieres-en-haye, France on May 9, 1966. He is the son of Robert L. Cusick and Loreine Despain. After graduating in 1985 from Mesa High School in Mesa, Arizona, he enlisted for five years in the U.S. Army. During this enlisted service he was selected for an Army Green to Gold scholarship and went on to attend the University of Arizona and the Army ROTC program. He earned a Baccalaureate of Science in Nursing graduating magna cum laude with induction into Sigma Theta Tau and Phi Kappa Phi International Honor Society and as a Distinguished Military Graduate in 1994. He received a Regular Army Commission in December 1994 and reentered active duty service as an officer and registered nurse. His background was in critical care nursing prior to admission into the United States Army Graduate Program in Anesthesia Nursing in 2001. He is married to Anja Kuhn and has 4 children.

This Thesis was typed by Captains Jeffrey Patrick Conroy and Warren Turley Cusick.