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13. ABSTRACT *(Maximum 200 words)*
Postoperative pain leads to increased morbidity, length of stay, and health care costs. Several studies have shown that preemptively administered N-methyl-D-aspartate (NMDA) antagonists, such as ketamine, are effective in decreasing perception of postoperative pain. To date, there have not been any human studies to investigate a gender difference in NMDA receptor antagonism. The purpose of this study was to compare the gender differences in the effects of preemptive ketamine on perceived pain in males and females undergoing selected ENT surgical procedures. This prospective, double-blinded study compared perceived pain in male and female subjects drawn from a convenience sample of patients at a major military medical center. The surgeries there patients were presenting for were tonsillectomy, adenoidectomy, tonsillectomy and adenoidectomy (T&A) and uvulopalatopharyngoplasty (UPPP). 41 subjects were randomly assigned to either a treatment group receiving .1mg/kg ketimine or a control group receiving a placebo of .9% saline. The study drug was administered between induction and incision. Pain perception following surgery was measured using a Numeric Rating Scale (NRS) on arrival to the post anesthesia care unit (PACU), and at four subsequent data points (1, 4, 12, 24 hours after PACU arrival time). ANOVA and Friedman tests were used to analyze the NRS scores. The ANOVA test did not show a significant difference ($p = .768$) in postoperative pain perception between males and females who received preemptive ketamine. The Friedman test did not show a significant difference ($p = .27$) in the level of postoperative pain perception within the groups over the five data collection points.

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A COMPARISON OF THE EFFECTS OF PREEMPTIVE ORAL DEXTROMETHORPHAN ON PERCEIVED POSTOPERATIVE PAIN IN MALE AND FEMALE PATIENTS UNDERGOING ARTHROSCOPIC KNEE SURGERY

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ABSTRACT

Preemptive use of N-Methyl-D-aspartate (NMDA) receptor antagonists, such as dextromethorphan, for reduction of postoperative pain has been well documented. Animal models have shown varied results in the efficacy of preemptive analgesia from NMDA receptor antagonists based on differences in gender. No research studies have been found in the literature to document gender differences in humans and the use of NMDA receptor antagonists. The purpose of this study was to identify gender differences in response to preemptive analgesia with NMDA receptor antagonists to help the anesthesia provider better manage patient's pain.

This was an Institutional Review Board (IRB) approved prospective, randomized, double-blinded, gender-stratified study design. Thirty-nine patients consisting of 6 females and 33 males were enrolled in this study. The experimental group received 1.5 milligrams per kilograms of dextromethorphan orally 40 minutes prior to surgery and the control group received a placebo 40 minutes prior to surgery. Pain was measured using the Numeric Rating Scale (NRS) recorded at baseline and four subsequent data points

(upon arrival to PACU, 1, 4, and 24 hours postoperatively).

An Analysis Of Variance (ANOVA) with repeated measures was used and significant differences were found in the placebo group between genders and reported pain ($p = .03$). There were no significant differences between male and female patients perceived pain who received preemptive dextromethorphan ($p = .16$). A Student's T-test was used and there was a gender difference for the first request for pain medication ($p = .01$). There were no significant differences between males and females for total pain medication taken in the first twenty-four hours ($p = .66$).

This study does support a gender difference in perceived pain. The results of this study, however, must be viewed with caution considering the representative sample size for gender comparison.

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CPHS LETTER OF APPROVAL

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NOTICE OF APPROVAL TO BEGIN RESEARCH January 15, 2003

HSC-SN-02-039 – "A Comparison of the Effects of Preemptive Oral Dextromethorphan on Perceived Pain in Male and Female Patients Undergoing Laparoscopic Surgery"
PI: Brent J. Persons, MSN Student

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

APPROVED: At a Convened Meeting

APPROVAL DATE: December 20, 2002 **EXPIRATION DATE:** November 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.

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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.

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CHAPTER I

Introduction

Pain is a universal and often under-treated problem. Human beings instinctively try to avoid pain. Unfortunately, in some instances pain may be unavoidable. Therefore, healthcare professionals try reducing or treating pain with medicines or other therapeutic measures. Recent pain research has focused on the preemptive use of drugs to reduce anticipated pain before it begins (Chia, Liu, Chow, & Lee, 1999; Dickenson & Sullivan, 1990; Fisher, Coderre, & Hagen, 2000; Helmy & Bali, 2001; Kawamata, Omote, Kawamata, & Namiki 1998; Plesan, Hedman, Xu, & Wiesenfeld-Hallin, 1998; Woolf & Chong, 1993). Further work of researchers has uncovered evidence that differences exist between males and females in their perceptions of pain (Kavaliers, Colwell, & Choleris, 1998; Sarton et al., 2000). Anesthesia care providers are primarily responsible for managing the pain that is associated with surgery. The anesthesia provider who understands and responds appropriately to gender differences in pain may be better able to manage patients' pain.

Statement of the Problem

Patients commonly experience pain following surgery. Even with current therapy, postoperative pain management is often ineffective (Filos & Lehmann, 1999). Therefore, research using new approaches to pain management is critical in determining how to better manage pain. Postoperative pain management may vary based on patient gender. Research indicates that gender differences may influence perception of pain and response to treatment of postoperative pain (Gear & Gordon et al., 1996; Gear & Miaskowsi et al., 1996).

Significance of the Problem

Pain can occur following all surgical procedures. Studies have found that somewhere between 50%-75% of people experience ineffective postoperative pain management, despite well-intentioned attempts by healthcare professionals to control pain (Filos & Lehmann, 1999; Warfield & Kahn, 1995). Pain directly influences postsurgical patients' ability to heal and creates further resource requirements for healthcare professionals and the industry (Beauregard, Pomp, & Choinier, (1998). Decreased pain levels increase patient satisfaction with surgery,

decrease length of stay, decrease admission rates to hospitals, and decrease the need for further intervention, freeing limited health resources for use by other patients in need. Ineffective pain management may additionally lead to unwanted side effects from analgesics.

Pain in Patients Receiving Arthroscopic Knee Surgery

This study examined pain management using pre-emptive analgesia in patients undergoing arthroscopic surgical procedures. Research has been directed at new techniques in reducing postoperative pain to accelerate patients' recovery from arthroscopic knee surgery. This research involved the use of local anesthetics, opioids, and nonsteroidal anti-inflammatory drugs (Reuben & Connelly, 1995; 1996).

Surgeons using arthroscopy have seen reduced perceived pain compared to open techniques (Highgenboten, 1982). There are many advantages of arthroscopic surgery including reduction of surgical trauma to the joint and its surrounding soft tissue, the ability to do the surgery in an outpatient setting, reduced postoperative pain and pain medications, and significant reduction in physical therapy

or the need to manipulate the knee (Highgenboten, 1982). In a survey conducted by Mancuso et al.(2001), they revealed nearly fifty-five percent of the patients undergoing knee surgery expected complete pain relief. Preemptive elimination of this postoperative pain can potentially improve patient outcomes and patient satisfaction.

Role of Dextromethorphan

Dextromethorphan has been studied extensively for its N-methyl-D-aspartate (NMDA) receptor antagonist properties. Multiple studies in animals and humans concluded that NMDA receptor antagonists were effective in preventing central sensitization and therefore reduced pain perception following nociceptive stimuli of surgical procedures (Bennett, 2000; Chia, Liu, Chow, & Lee, 1999; Henderson, Withington, Wilson, & Morrison, 1999; Price, Mao, Frenk, & Mayer, 1994; Woolf & Thompson, 1991; Wu et al., 1999).

Evidence of Gender Differences

Animal studies suggest that gender plays a role in pain perception, although conflicting results have been reported as to which gender better mediates pain perception

(Gear, Miaskowski et al., 1996; Kest, Sarton, & Dahan, 2000; Sarton et al., 2000). Human studies have examined the gender differences to pain response with opioid mediated and nonsteroidal anti-inflammatory drugs (NSAIDS). In human opioid studies examining gender differences, stronger evidence points to greater potency with slower onset and offset in females as compared to males (Sarton et al., 2000). Researchers examining NSAIDS have demonstrated stronger evidence for better analgesic effect in male as compared to female patients (Walker & Carmody, 1998). In animal studies using mice, researchers have examined the NMDA receptor response to pain with stronger evidence that male mice antagonize pain better at the NMDA receptor (Kavaliers et al., 1998).

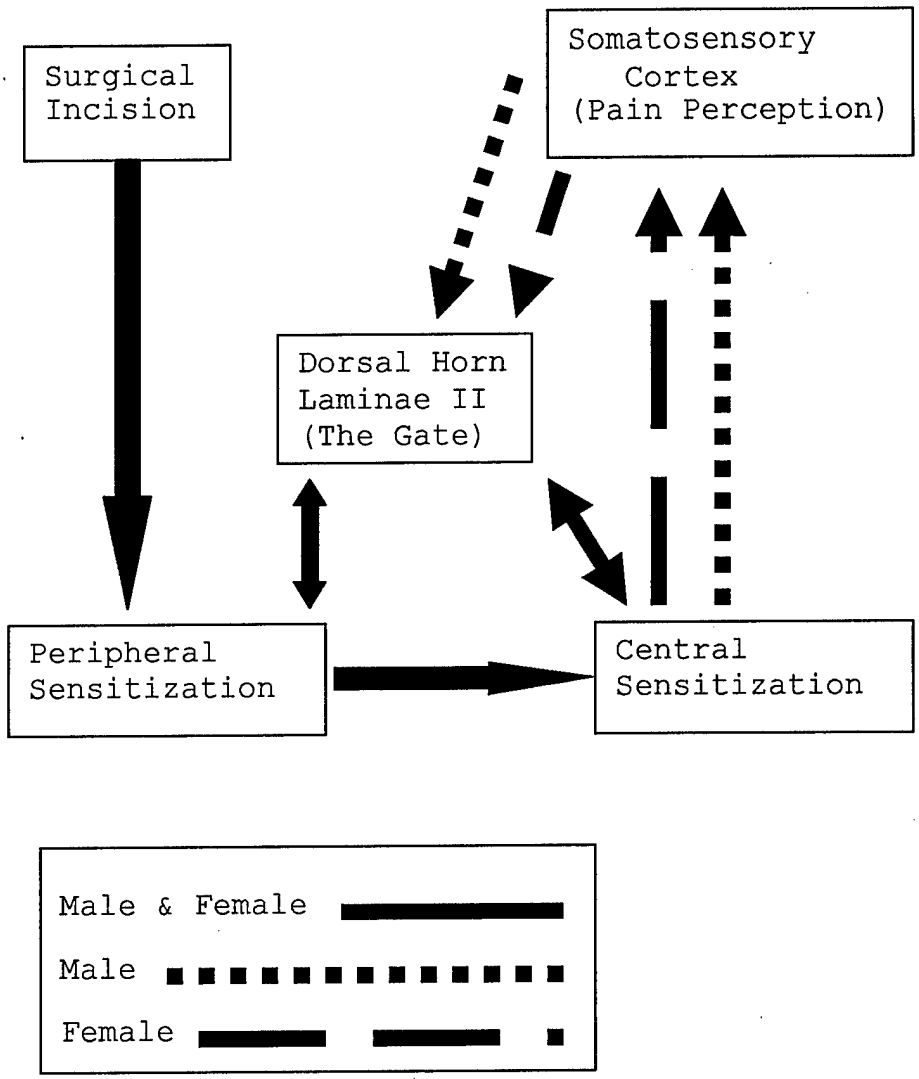
The review of the literature revealed no research that could be found examining the gender differences related to preemptive administration of dextromethorphan in postoperative perception of pain in humans. This study added to the body of knowledge by comparing the effects of preemptive oral dextromethorphan on perceived postoperative pain in male and female patients undergoing elective arthroscopic knee surgery.

Theoretical Framework

The theory that guided this research study was the gate-control theory on pain. The gate-control theory is the foundation for explaining how an individual perceives physiological pain. In surgical pain, a stimulus, such as a surgical incision, stimulates a peripheral receptor that causes a nerve signal to travel along nerve fibers to the spinal cord. The pain signal is transferred to the spinal cord where it ascends to the somatosensory cortex where pain is perceived (Wall, 1988). This exemplifies a direct approach that explains how pain is elicited during surgical procedures. Melzack and Wall introduced the gate-control theory of pain in 1965. However, clinical research has shown that the gate-control theory does not completely explain the perception of pain. Pain is also influenced by peripheral and central sensitization (Cook, Woolf, Wall, & McMahon, 1987; Woolf, 1983; Woolf & Walters, 1991) (*See figure 1).*

The use of dextromethorphan in preemptive analgesia for postoperative pain inhibits central sensitization. Central sensitization is created through surgical pain.

Figure 1. Gate-control theory of pain control.



The gate control-theory on pain links the concepts of central sensitization and gender differences. Gender differences are expressed through variations in pain sensitivity, physiologic response to pain, and metabolism.

Peripheral sensitization is induced by neurohumoral alterations at the site of injury and regions nearby. The injured tissue releases a variety of neurotransmitters, making the peripheral receptor more receptive to painful stimuli. This results in a reduction in the threshold and increased transmission of primary afferent nociceptors (Woolf & Walters, 1991). The increase of pain transmission to the spinal cord influences the induction of central sensitization in the spinal cord.

Central sensitization influences the pain pathway. C. J. Woolf in 1983 first published the concept of central sensitization. His early research on central sensitization revealed that brief activation of C nerve fibers resulted in a marked and prolonged increase in the flexion withdrawal reflex in spinal-decerebate rats (Woolf, 1983).

Central sensitization takes place in the spinal cord dorsal horn in Laminae I and II. The increase in pain transmission along nerve fibers due to peripheral

sensitization results in a hypersensitivity response to subsequent stimuli (Woolf & Chong, 1993). Central sensitization produces an expansion of the receptive field, an increase in magnitude and duration of response, and a reduction in threshold (Cook, Woolf, Wall, & McMahon, 1987). Central sensitization results in increased pain transmission from the spinal cord to the brain where it is perceived. The induction and maintenance of central sensitization is dependent on NMDA receptor activation (Woolf & Thompson, 1991).

The NMDA receptor's mechanism of action was the focus in this study for using dextromethorphan in preventing postoperative pain. Dextromethorphan is an NMDA antagonist that binds to the receptor and inhibits central sensitization. Preemptive treatment prevents the spinal cord from reaching a hyper-excitable state where previous non-painful stimuli creates pain perception (Wall, 1988). The degree of central sensitization inhibition may be dependent upon gender differences. Presently there are no published human studies that have evaluated gender differences for central sensitization.

Purpose of the Research

The purpose of this research is to compare the effects of preemptive oral dextromethorphan on perceived postoperative pain in male and female patients undergoing elective arthroscopic knee surgery.

Definition of Terms

Pain.

Conceptual definition: Pain is a "noxious sensory and emotional experience in reaction to potential or real tissue damage or as a result of disease" (Garrett & McShane, 1999). Operational definition: Pain is operationally defined as the pain score reported by patients on the Numerical Rating Scale (NRS).

Postoperative.

Conceptual definition: Postoperative is the period of time immediately following a surgical procedure (Mish, 1989). Operational definition: Postoperative is operationally defined as the first twenty-four hours following completion of the patient's surgical procedure.

Preemptive analgesia.

Conceptual definition: Preemptive analgesia reduces the development of postoperative pain by blocking pain

pathways before central sensitization occurs (Melzack, Coderre, Katz, & Vaccarino, 2001). Operational definition: Preemptive analgesia is operationally defined as the administration of oral dextromethorphan at 1.5 mg/kg forty-five minutes prior to surgery.

Research Hypothesis

The following are the research hypothesis in this study:

1. There is a difference in the level of postoperative pain perceived by females as compared to males who receive preemptive oral dextromethorphan prior to undergoing an arthroscopic knee procedure.

2. There is a difference in the level of postoperative pain perceived by females as compared to males undergoing an elective arthroscopic knee procedure.

Null Hypothesis

There is no difference in the level of postoperative pain perceived by females as compared to males who receive preemptive oral dextromethorphan prior to undergoing an arthroscopic knee procedure.

Assumptions

The assumptions of this study are:

1. Surgical procedures create postoperative pain at the

surgical site.

2. Pain is a measurable phenomenon.

3. Level of noxious stimulus will be relatively uniform across study population.

4. Patient will report their pain relative to the level of perceived pain.

Limitations

The limitation of this study is: Selection of patient samples by convenience sampling from a military medical facility and limiting the study to specific types of surgery limits the ability to generalize findings to other patient populations and to other surgical procedures.

Summary

Postoperative pain remains a problem because treatments for pain are not entirely effective. New treatments for pain must examine the variables that influence pain, such as gender. Providing preemptive pain therapy is supported by the gate-control theory and has been shown to reduce patient pain and improve overall patient care. Recent research findings support the use of dextromethorphan as preemptive analgesia to decrease patient's postoperative pain.

The study examined some of the gender differences that may exist in postoperative pain perception. The value of

understanding these possible differences may impact the anesthesia provider's choice to use preemptive analgesic. This study compared the effects of preemptive oral dextromethorphan on perceived pain in male and female patients undergoing elective arthroscopic knee procedures.

CHAPTER II

Review of Related Literature

Pain

All organisms, including humans, encounter threats to their physical integrity in the environment and defensive responses are found in all major animal phyla. In the animal kingdom, virtually all animals share two basic needs: the need to escape from a source of injury and the need to protect healing parts from further damage (Woolf & Walters, 1991). In both instances, the concept of pain is involved. Pain is conceptually defined as a "noxious sensory and emotional experience in reaction to potential or real tissue damage or as a result of disease" (Garrett & McShane, 1999).

Postoperative pain continues to be insufficiently treated following surgical procedures and it continues to be a primary patient concern. A survey conducted of inpatient and outpatient surgery patients, found that 59% of patients' primary concern prior to surgery was postoperative pain (Apfelbaum, Gan, & Chen, 2000; Gan, Apfelbaum, & Chen, 2000). Modern medicine has made great efforts to understand the phenomenon of pain and provide

better therapy; yet postoperative pain management remains inadequate. Researchers have estimated between 50%-75% of postoperative patients complained of inadequate pain control (Warfield & Kahn, 1995; Filos & Lehmann, 1999). Pain in the first 24 to 48 hours following same day surgery can be as high as 63% to 100% (Mackintosh & Bowles, 1998). One variable in postoperative pain management may be gender differences in perception of pain and response to treatment of postoperative pain (Kavaliers & Innes, 1992). Research with medications and new techniques needs to be conducted to determine how to better manage postoperative pain.

In 1999, the Joint Commission on Accreditation of Healthcare Organization introduced new pain management standards that were scored for compliance. The recent emphasis on pain management stresses the importance in understanding basic pain phenomena and advances in pain management (Doyle, 2001). However, healthcare practitioners are often ineffective in providing universal pain control (Kuhn, Cooke, Collins, Jones, & Mucklow, 1990). In order to successfully treat pain, the concept of pain must be reviewed. This involves the Gate-Control theory on pain, the pain pathway, and central sensitization.

Postsurgical Pain Significance

Unfortunately, postsurgical pain is often expected by patients and is not reported. Up to 46% of patients would rather suffer than report their pain (Scott & Hodson, 1997). Pain directly influences postsurgical patients' ability to heal. Pain can increase sympathetic outflow leading directly to decreased metabolic catabolism and normal muscle function (Filos & Lehmann, 1999; Rawal, 1998; Rosenberg & Kehlet, 1999). Pain also creates further resource requirements for healthcare professionals and the industry. Chung, Ritchie, and Su (1997) found in their study that 10% of unplanned admissions were due to uncontrolled pain. Researchers have also found that the length of stay in the postanesthesia care unit (PACU) was increased due to severe pain, and discharge time in general was increased because of pain (Chung et al., 1997).

Pain in Arthroscopic Knee Surgery Patients

This study recruited subjects scheduled for arthroscopic knee procedures so that the level of noxious stimuli would be relatively uniform. Arthroscopic knee procedures reduce postoperative pain and complications

because it allows surgeons to perform a less invasive procedure than the traditional open procedure (Highgenboten, 1982).

Pain can significantly affect activities of daily living. Beauregard, Pomp, and Choinier (1998) found that about one half of patients report that pain interferes with three or more daily activities.

Theoretical Framework

The foundation for scientific research in pain is the Gate-Control Theory on Pain. In 1965, Ronald Melzack and Patrick Wall proposed that pain involves nerve signals that travel from the site of injury along A-delta and C nerve fibers to the dorsal horn of the spinal cord (Wall & Melzack, 1994). This area is known as the substantia gelatinosa. At this location, the afferent impulses from the small excitatory nerve fibers come into contact with efferent impulses from large inhibitory nerve fibers. If the excitatory impulses are strong enough, they override the inhibitory impulses at the substantia gelatinosa and the gate is opened. The pain signals travel up the spinal cord to the brain and pain is perceived.

Synaptic contacts between neurons were assumed to be stable and sensory processing was considered to reflect fixed patterns of anatomical connections (Woolf, 1996). Overall, a defined stimulus would always elicit a predictable response and the neuron's receptive fields would remain unchanged. While this may seem a direct approach that easily explains pain, research has shown that the Gate-Control Theory needed modification.

"The most important modification in discussing pain is that the nervous system is not a hard-wired, line-labeled system, but instead is capable of plasticity: the ordered alteration of structure or function due to development, experience or injury" (McQuay & Dickenson, 1990). Plasticity can be induced over a remarkably short time (Dickenson, 1995). Clinically this is evident in the recurrence of pain after cordotomy and the existence of phantom limb pain. Phantom limb pain can be described as the same type of pain felt in the extremity before it was amputated. Neither of these examples can be explained without the idea that the nervous system can change, re-establishing pain inputs, and possibly remembering painful events (McQuay & Dickenson, 1990). The nervous system is capable of plasticity; therefore, it is important to understand how the pain pathway is implemented.

Normal Pain Pathway

The pain pathway involves components of the peripheral and central nervous system (CNS). Spinal and supraspinal elements also have key roles. The pain pathway is initiated when the body is innervated by a noxious stimulus. The skin, muscle and tendon, periosteum and synovium, heart and blood vessels, and the viscera are all innervated by peripheral nociceptors that are specialized to respond to stimuli that cause or threaten to cause, tissue injury (Bennett, 2000). The stimuli can be chemical, thermal, or mechanical (Dahl, Erichsen, Fuglsang-Frederiksen, & Kehlet, 1992). The nociceptors transduce the noxious stimuli signal to myelinated A-delta and unmyelinated C fiber afferent neurons. After the nociceptors have transduced the noxious stimuli to the respective nerve fiber, the pain impulse is transmitted to the spinal cord.

The A-delta and C nerve fibers transmit their impulses to their respective cell bodies located in the dorsal root ganglion. Nerve fibers, called axons, branch from the cell body and terminate at the dorsal horn in spinal cord segments labeled Laminae I, II, and V (Bonica, 1990). The axons then synapse with second order pain fibers (Besson,

1988). The pain impulse travels rosterally along one of the spinal cord pathway tracts to the thalamus. The major pain tract is the spinothalamic tract. The pain impulse travels to the thalamus and reaches the somatosensory cortex. This is where the quality of the pain and each person's perception of pain is based on that interpreted (Besson, 1988). In undamaged tissue, activation of nociceptive afferent nerve fibers generally results in a proportional relationship between the stimulus and the response (Raja, Meyer, & Campbell, 1988). This relationship is altered in the presence of tissue damage (Dahl et al., 1992). The altered relationship between stimulus and response appears with postoperative pain.

Postoperative Pain

Postoperative pain is associated with peripheral tissue damage that is produced during surgery. Peripheral tissue damage can lead to a change in sensitivity that results in a reduction in the intensity of stimulation necessary to initiate pain. Therefore, stimuli that normally do not produce pain are now capable of triggering a pain response. This is defined as allodynia. Two other

clinical manifestations, primary and secondary hyperalgesia, also exist with clinical pain.

With primary hyperalgesia, there is an exaggerated response to noxious stimuli where the stimulus-response curve is shifted to the left (Bennett, 2000). In secondary hyperalgesia, there is a spread of hypersensitivity to non-injured tissue (Treede, Meyer, Raja, & Campbell, 1992). In both instances, two mechanisms function to produce these changes in sensitivity found in clinical pain: peripheral sensitization and central sensitization, (Woolf & Walters, 1991).

Peripheral Sensitization

Primary afferent nociceptors have a high threshold level that must be met in order before a noxious stimuli impulse is relayed to afferent nerve fibers. Peripheral sensitization involves a reduction in the threshold level and an increase in the gain of the transduction processes of the primary afferent nociceptors (Woolf & Walters,1991). Several sources of inflammatory mediators contribute to peripheral sensitization (Woolf & Walters, 1991). Histamine, serotonin, hydrogen ions, cytokines, nerve growth factors, prostaglandins, neuropeptides, bradykinin,

and catecholamines generate a sensitizing "soup". The chemicals appear to act synergistically to alter the sensitivity of afferent nociceptors (Lang, Novak, Reeh, & Handwerker, 1990). Therefore, the threshold level for nociceptor stimulation is decreased and transmission of painful stimuli is increased to the spinal cord.

The induction and maintenance of surgical pain will be enhanced in inflammatory states where the increased impulses from the afferents will facilitate spinal excitation (Dickenson, 1995). The induction of peripheral sensitization leads to activating central sensitization.

Central Sensitization

Central sensitization includes changes in the receptive fields of spinal neurons after an increase in excitability produced by peripheral nociceptor inputs. This, in turn, leads to a hypersensitivity response to subsequent stimuli (Woolf & Chong, 1993). The first published research on central sensitization revealed that brief activation of C nerve fibers resulted in a marked and prolonged increase in the flexion withdrawal reflex in spinal-decerebrate rats (Woolf, 1983). Because peripheral sensitization lowered the threshold level for pain impulses

to be transmitted, repeated constant C nerve fiber stimuli resulted in responses of the deep dorsal horn neurons to increase in magnitude despite a steady input into the spinal cord (Davies & Lodge, 1987). Lorne Mendell first observed this phenomenon in 1965. Lorne Mendell and Pat Wall, working together, named this phenomenon "wind-up" (Mendell, 1966).

Wind-up needs a certain frequency of stimulation to be produced (Dickenson, 1995). When produced, wind-up can increase amplitude responses of dorsal horn neurons 20-fold. Wind-up can also prolong responses even after the peripheral noxious stimulus is stopped. The initiation of peripheral sensitization leads to the activation of central sensitization with the end results being postoperative pain.

Postoperative pain is manifested through A-delta and C nerve transmission due to peripheral sensitization and through A-beta nerve transmission due to spinal cord plasticity (Li, Simone, & Larson, 1999). Spontaneously discharging nociceptors will give rise to ongoing pain due to increased afferent nerve fiber traffic to Laminae I and II in the dorsal horn (Besson, 1988). In these laminae the

primary afferent nerve fibers synapse with second order neurons. The primary afferent neurons release many substances at the spinal cord level, including a number of peptides and the excitatory amino acids glutamate and aspartate.

Spinal cord neurons express three subtypes of glutaminergic receptors: the N-methyl-D aspartate subtype, the kainite/AMPA subtype, and the metabotropic subtype (Bennett, 2000). The continued release of glutamate results in its binding to the NMDA receptor (Battaglia & Rustioni, 1988). There is evidence that NMDA receptors are involved in pain perception in the brain (Klepstad, Maurset, Moberg, & Oye, 1990).

NMDA Receptors

The induction and maintenance of central sensitization is dependent on NMDA receptor activation (Woolf & Thompson, 1991). Activation of the NMDA receptor requires the binding of glutamate, the presence of glycine, and the means to remove the physiological levels of magnesium that normally block the channel. Protein kinase binds to the NMDA receptor, phosphorylates it, and partially removes the magnesium channel blockade (see figure 2). The removal of

Figure 2. The NMDA receptor function.

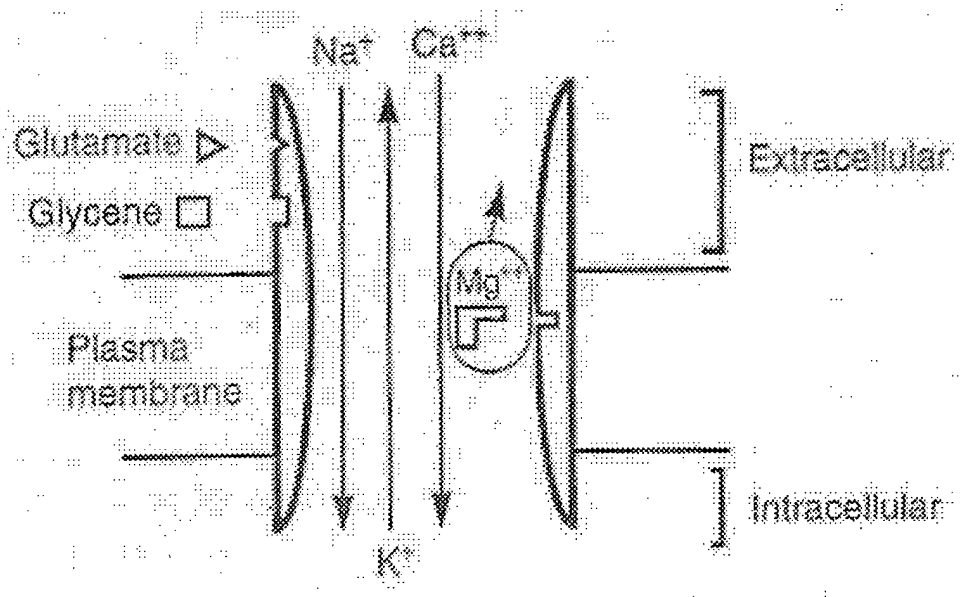


Figure 2. Protein kinase feeds back onto the NMDA receptor, phosphorylates it, and partially removes the magnesium channel blockade. Glutamate is now able to generate an inward current of sodium and calcium and potassium extracellularly. From "The pathophysiology of pain," by N. Garrett & F. McShane, 1999, *AANA Journal, 67,* 351. Copyright 1991 by American Association of Nurse Anesthetists. Reprinted with permission of the author.

magnesium results in an inward current of sodium and calcium and potassium extracellularly. The outcome is increased nerve transmission via the spinothalmic tract to the brain where it is invaded with nociceptive input (Thompson, King, & Woolf, 1990). Inhibiting central sensitization may, therefore, decrease postoperative pain.

Central sensitization inhibition can be implemented with preemptive analgesia. Preemptive analgesia is where the afferent nociception input that implements central sensitization is prevented from gaining access to the central nervous system. Therefore, there will be a slighter amount of postoperative pain experienced associated with tissue trauma (Wall, 1988). Because central sensitization involves the NMDA receptor, it can be hypothesized that an NMDA receptor antagonist may modulate the hypersensitivity of spinal cord.

NMDA Antagonist Function

There is universal agreement that NMDA receptor antagonists suppress central sensitization in experimental animals (Bennett, 2000). Competitive and non-competitive NMDA antagonists prevent wind-up by C nerve fiber stimulation in vivo in the rat model (Dickenson & Sullivan,

1990). The NMDA antagonists attach to the NMDA receptor binding sites. The NMDA receptor complex has various binding sites that allow different substances to regulate its activity. Non-competitive antagonists bind to the phencyclidine (PCP) site inside the NMDA receptor channel and block the influx of calcium once the NMDA receptor has been activated by glutamate (Fisher, Coderre, & Hagen, 2000).

NMDA Antagonists

Dextromethorphan, an NMDA antagonist, at clinically relevant oral doses, binds to the PCP site of the NMDA receptor complex (Fisher et al., 2000). Dextromethorphan has been shown to reduce temporal summation of burning, throbbing, or aching in humans (Price et al., 1994). Oral dextromethorphan administered at 120 mg reduced secondary hyperalgesia in humans (Ilkjaer, Dirks, Brennum, Wernberg, & Dahl, 1997).

Ketamine is an arylcyclohexylamine analogue of phencyclidine hydrochloride (PCP). This drug is a racemic compound, with the S (+) isomer causing more profound sedation and analgesia than the R (-) enantiomer. Ketamine has a low affinity for the NMDA ion channel, with an

apparent degree of antagonism determined by the state of the receptor. This agent's blockade of the NMDA receptor is much greater when the receptor is hyperpolarized (Muir & Lees, 1995). Ketamine is proven to be safe for clinical use and is a commonly administered analgesic agent. A subanesthetic dose of ketamine will produce impaired memory registration, altered sensory perception, and hallucinations (Muir & Lees, 1995). Its use as a preemptive analgesic has been studied with mixed results.

Amantadine is a 1-amino-3, 5-dimethyl-adamantane derivative, that has been used clinically as an antiviral agent and more recently this agent has been used in clinical trials to examine its analgesic effects in patients with chronic neuropathic pain. Amantadine has antiparkinson properties, which have been used to improve muscle rigidity and akinesia (Schwab, England, Poskanzer & Young, 1969). Amantadine is a noncompetitive NMDA receptor antagonist. This agent also binds at the PCP site of the NMDA receptor (Schwab, et al., 1969).

Clinically, amantadine's antiviral affects have several purposes. This drug has been used in the prevention of the recurrence of sacral dermatomal neuralgic pain associated

with herpes simplex, reduction in pain associated with herpes zoster and prevention of postherpetic neuralgia (Galbraith, 1973). Researchers have examined amantadine's effect in neuropathic pain patients, since the discovery that amantadine is a NMDA antagonist. Through studies conducted by Eisenberg and Pud (1998), it was discovered that amantadine completely abolished spontaneous pain, mechanical allodynia, and hyperalgesia in patients with chronic neuropathic pain.

Another 1-amino-3, 5-dimethy-adamatane derivative that has been used in clinical trials is memantine. This drug has also clinically been used for the treatment of spasticity, dementia and Parkinson's disease (Fisher, Coderre, & Hagen, 2000). Another NMDA receptor antagonist is Memantine, which binds at the PCP site with a relatively low affinity. This agent has been shown to ease the progression of or reverse nociceptive behavior in animal with neuropathic pain (Fisher, et al., 2000).

Magnesium is frequently used in obstetrics as a tocolytic for preterm labor and to increase the seizure threshold of a patient with pregnancy induced hypertension. Its use as a noncompetitive NMDA antagonist is not yet

commonplace in clinical practice. In a voltage-dependent manner, intracellular magnesium blocks the NMDA ion channel but extracellular magnesium behaves like a noncompetitive NMDA antagonist (Muir & Lees, 1995).

Mk-801, CGS19785 and LY274614 are strong NMDA receptor antagonist. These drugs have distinct psychomimetic effects and are potentially neurotoxic (Plesan et al., 1998). For this reason, these drugs are unavailable for clinical use.

Preemptive Dextromethorphan in Humans

Clinical research on dextromethorphan's effectiveness in reducing postoperative pain in human studies has mixed results (Helmy & Bali, 2001; Rose, Cuy, Cohen, & Schreiner,1999). The variability in different studies revolve around the amount and route that dextromethorphan was administered preoperatively. The most popular route is oral. Other studies have used intramuscular and intravenous routes of administration. The dosage amount of Dextromethorphan ranges from 30 milligrams (mg) to 280 mg. The mixture of the variables between route of administration and the dosage amount of dextromethorphan has led to mixed reviews of dextromethorphan's effectiveness. A review of the clinical studies was done by

these categorical variables.

Intramuscular Dextromethorphan Usage in Humans

Clinical studies implementing intramuscular injection of dextromethorphan indicate it is effective in reducing pain. A study conducted by Wu et al. (1999) found that preemptive administration of 40 mg dextromethorphan IM was related to a significant reduction in postoperative pain for laparoscopic cholecystectomies. Worst pain scores ($p < .01$), total meperidine consumption ($p < .01$), and amount of time to first meperidine injection following completion of surgery ($p < .01$) were statistically significant for postoperative analgesia. Wong et al. (1999) found a significant relationship between preemptive administration of 40 mg of dextromethorphan IM and a reduction in postoperative pain in patients undergoing modified radical mastectomy procedures. Helmy and Bali (2001) found that 100 mg of IM dextromethorphan administered preoperatively was related to a significant reduction of postoperative pain in elective upper abdominal procedures. The total amount of postoperative meperidine consumption ($p < .01$) and time from extubation to first request for PCA ($p < .01$) was statistically significant.

These studies indicate that dextromethorphan is effective in reducing postoperative pain if given intramuscularly before surgery.

Intravenous Dextromethorphan Usage in Humans

Intravenous administration of dextromethorphan has also been shown to alleviate postoperative pain. Chia et al.(1999), examined intravenous dextromethorphan's effectiveness in reducing postoperative pain when administered at a dosage amount of 5 mg/kg (average of 280 mg per patient). Postoperative daily morphine consumption was significantly reduced ($p < .01$) up to 48 hours after the surgical procedure for patients who received preoperative dextromethorphan. Even at a high dosage of dextromethorphan, related side effects of sedation, distorted vision, feeling drunk, and ataxia were not reported in the study. Unfortunately, intravenous administration of dextromethorphan is not available for clinical trials in the United States. Therefore, based on the availability, oral dextromethorphan was selected for use in this study.

Oral Dextromethorphan Usage in Humans

In studies using oral dextromethorphan preoperatively,

the dosage ranged from 15 mg to 150 mg. Researchers found significant results in reducing postoperative pain when a minimum dose of 30 mg oral dextromethorphan was administered (Caruso et al., 1998; Grace et al., 1998; Ilkjaer et al., 1997; Kawamata et al., 1998; Minn, Nelson, Brahim, & Caruso, 1998). Minn et al. (1998) found no significant difference in the reduction of postoperative pain in patients who received 60 mg oral dextromethorphan as compared to those patients who received 120 mg oral dextromethorphan preemptively for oral surgery. Grace et al. (1998) found that patients receiving 60 mg oral Dextromethorphan preoperatively had reduced intraoperative morphine requirements but not postoperative morphine requirements. A study by Ilkjaer, Bach, Nielsen, Wernberg, and Dahl (2000) indicated that 150 mg of oral dextromethorphan given preoperatively reduced postoperative pain up to four hours ($p = .02$) for total abdominal hysterectomy procedures. Findings from these studies indicate that preemptive dextromethorphan reduces post-operative pain.

However, some studies involving oral dextromethorphan have not demonstrated significant results in postoperative

pain reduction. McConaghy, McSorley, McCaughey, and Campbell (1998) found no difference in postoperative pain for patients who received 54 mg oral dextromethorphan preoperatively for total hysterectomy procedures. However, the dosage was split into two 27 mg oral doses instead of administering 54mg in one dose.

Rose et al. (1999) found no difference in postoperative pain in children who received 0.5 mg/kg and 1.0 mg/kg of oral dextromethorphan prior to adenotonsillectomy procedures as compared to receiving a placebo in reducing postoperative pain. However, the surgical procedures were different between the above-mentioned studies and the effects of gender on postoperative pain perception were not considered.

NMDA Receptor Antagonists and Knee Surgery

The number of studies regarding NMDA receptor antagonists and knee surgery are limited. Only one clinical study examined the use of dextromethorphan for preemptive analgesia and knee surgery. Wadhwa, Clarke, Goodchild, and Young (2001) examined oral dextromethorphan as an adjunct to patient controlled analgesia with morphine after knee surgery. Preemptive oral dextromethorphan resulted in 29

percent significant reduction for postoperative morphine requirements ($p < .05$). Two other studies involved arthroscopic knee procedures and the use of ketamine; another NMDA antagonist. Menigaux et al.(2000) study examined the use of ketamine on postoperative pain after anterior cruciate repair. Less postoperative pain requirements ($p < .01$) and better first knee flexion ($p < .05$) was noted. Menigaux et al.(2001) study involved the use of ketamine as preemptive analgesia with outpatient knee arthroscopy. Pain scores were significantly lower ($p < .05$) and morphine titration was less ($p < .05$) when ketamine was administered prior to the surgical procedure. Magnesium sulfate, another NMDA receptor antagonist, reduces intra and postoperative analgesic requirements ($p < .05$) when given preemptively for arthroscopic knee procedures (Koinig, et al., 1998). The above listed studies did not consider the effects of gender on postoperative pain perception. A clinical study that controls for gender differences in response to dextromethorphan, might partially explain variations in pain perception.

Gender Differences

Animal Studies

The majority of research on gender differences in relationship to pain used rodents as the experimental subjects, and studied opioids and opioid receptors. Pain can be measured by observable movement in response to nociceptive stimuli. Antinociceptive effects are measured by latency of response to a nociceptive stimulus. The majority of research on animals indicated that males responded with greater sensitivity to the analgesic effects of opioids (Boyer, Morgan, & Craft, 1998; Cicero, Nock, & Meyer, 1996; Kavaliers & Innes, 1992; Kepler, Standifer, Paul, Pasternak, & Bodnar, 1991; Krzanowska & Bodnar, 1999). Attempts have been made to explain this gender difference in response to exogenous and endogenous opioids.

Kavaliers and Innes (1992) suggest there are endogenous opioid modulating systems that function differently based on gender. Boyer et al.(1998) injected morphine into the ventromedial medulla of male and female rats to determine if gender differences are expressed in the central nervous system. Findings from this study suggested that male rats were more responsive to morphine and not necessarily less sensitive to noxious stimuli. Krzanowska and Bodnar (1999) took this concept of injecting

morphine into the central nervous system a step further by performing gonadectomies on the rats to evaluate hormonal influences. They found that males were more responsive to morphine and that ovariectomized females had enhanced antinociception at higher doses of morphine.

Cicero et al. (1996) and Kepler et al. (1991) conducted studies that involved gonadectomies of their subjects and found that males were more sensitive to morphine, and that there was no significant affect from gonadectomy. Their findings suggest that gender differences and morphine sensitivity are not related to sex hormones.

Mogil, Sternberg, Kest, Marek, and Liebeskind (1993) concluded that there might be an estrogen-dependent mechanism of swim stress-induced analgesia in female mice. Mogil et al. (1993) found that the swim stress-induced analgesia was antagonized by naloxone and dizocilpine (NMDA antagonist) in males, but not females in 20 degrees Celsius water. In 15 degrees Celsius water, swim stress-induced analgesia was attenuated by dizocilpine in males, but not females. Ovariectomized mice are sensitive to dizocilpine antagonism of swim stress-induced analgesia. Estrogen therapy restored the normal female insensitivity to dizocilpine. Mogil et al. (1993) attempted without success to localize the specific trait on the female chromosome

that expressed female-specific stress-induced analgesia mechanism in mice.

Multiple rodent experiments involving NMDA antagonists demonstrate that analgesia is antagonized in males, but not females (Kavaliers & Choleris, 1997; Kavaliers et al. 1998; Lipa & Kavaliers, 1990). In contrast to the findings of Mogil et al. (1993), Kavaliers et al. (1998) stated there were no variations in the stress-induced analgesia or the basal nociceptive sensitivity over the relatively short estrous cycle of female deer mice.

Sershen and Hashim (1998) used the NMDA antagonist NPC 12626 to antagonize the kappa (U69,593) opiate-induced analgesia in male mice without a significant influence on female mice analgesia. Sershen and Hashim suggest that there is less kappa inhibition of NMDA-evoked dopamine release in female mice striata. Sershen and Hashim also noted there were no estrous cycle-related changes to account for the gender differences in kappa opiate-induced analgesia.

Kest, Wilson, and Mogil (1999) examined the effects of genotype on gender differences in supraspinal morphine analgesia. The researchers were able to breed a strain of mice in which the females were more than five fold more sensitive to morphine analgesia than the males of that

breed.

Bartok and Craft (1997) found varying gender differences dependent upon time, dose, and which selective opioid was used. They found gender differences with antinociceptive effects of kappa and delta opioids, but not with mu opioids. Peak effects of U69,593 and DPDPE occurred earlier in females than males. Greater hot-plate antinociception was seen in males more than females with delta opioids.

Human Studies

Sarton et al. (2000) concluded that morphine was more potent for women, but had a slower onset and offset than in men. The observed gender differences were not related to pharmacokinetics of morphine as the concentration of morphine and its metabolites did not differ between men and women. The results indicated a pharmacodynamic origin for the gender differences in morphine-induced analgesia.

Gear, Miaskowsi et al. (1996) and Gear, Gordon et al. (1996) suggested that kappa-opioids are more effective for women than for men. The first research used pentazocine and demonstrated significantly better analgesia for women as compared to men. The second study this research team conducted used nalbuphine and butorphanol, which were more efficacious for producing analgesia in women than in men.

In contrast to the previous studies, Walker and Carmody (1998) found that nonsteroidal anti-inflammatory drugs (NSAIDS) were less effective for women. Walker and Carmody hypothesized that electrical stimulation created neurogenic inflammation by means of substance P, which then activates prostaglandin synthesis. Since there is no gender difference in NSAIDS suppression of inflammation, Walker and Carmody suggest that analgesic and anti-inflammatory actions of NSAIDS are at separate sites.

Lester, Lefebvre, and Keefe (1994) conducted two studies polling college students participating for partial fulfillment of a psychology course. The first study examined gender and family pain history related to pain intensity (n=252). The second study examined how those gender and family pain history related to pain intensity, location and activity interference (n=206). The results indicated that women reported a greater number of sites of pain.

It is difficult to obtain quantitative data on psychosocial variables. Otto and Dougher (1985) compared personality factors and pain responses. The subjects were classified the subjects as masculine or feminine based on a questionnaire. The common finding was higher pain thresholds and tolerances for men than women. Most of the

difference was based on gender; however there was a significant correlation between pain thresholds and masculinity-femininity scores for men. The significance of that finding is that very masculine men may show a gender difference in pain thresholds and feminine men may obscure the difference (Otto & Dougher, 1985).

Summary

Postoperative pain results in decreased comfort, decreased ability to heal, and increased sympathetic outflow in postoperative patients. Even though a plethora of research has been conducted in this field, postoperative pain control continues to be inadequate for up to 75% of patients (Warfield & Kahn, 1995). Before examining new ways to adequately control postoperative pain, researchers must consider the gate-control theory on pain, pain pathways, central sensitization, and gender differences. This study compared the effects of preemptive oral dextromethorphan on perceived postoperative pain in male and female patients undergoing arthroscopic procedures.

CHAPTER III

Methodology

Postoperative pain remains a problem even when using less invasive surgical procedures. The purpose of this study was to compare the effects of preemptive oral dextromethorphan on perceived postoperative pain in male and female patients undergoing arthroscopic procedures. This chapter describes the population, sample, setting, the instrumentation, the procedures used for data collection, protection of human subjects, and study design.

Population, Sample, and Setting

The sample population was derived from male and female patients electing to undergo elective arthroscopic knee procedures. The setting was a major military medical center on the West Coast. The facility provides all major surgical services for active duty personnel, retirees, and family members for all branches of the United States Armed Forces.

Subjects of the study were selected using a convenience sample of patients who met the inclusion criteria. Inclusion criteria consisted of males and females who were at least 18 years of age and scheduled for one of the elective arthroscopic knee procedures. Subjects had an

American Society of Anesthesiologists (ASA) physical status I, II and III, and were be competent to give informed consent.

Patients were excluded if they were allergic to dextromethorphan, using monoamine oxidase inhibitors (MAOIs), taking analgesic medications, or were non-English speaking subjects. Other exclusion criteria included subjects who were pregnant, incompetent, or had a history of psychiatric illness or substance abuse.

Power analysis indicated a minimum of 68 subjects were required. This was based on a previous study by Wu, Yu, Yeh, Liu, Li, Yuan, Ho, and Wong (1999) that studied the effect of preincisional dextromethorphan treatment decreased postoperative pain and opioid requirement after laparoscopic cholecystectomy. The study revealed significant statistical results with a large effect size(*es*) for total meperidine consumption (*es* 8.67), times to first postoperative meperidine injection (*es* 1.95) and for higher visual analog pain scores (*es* 6.67). There were significant statistical results with a large effect size in human studies concerning dextromethorphan as preemptive analgesia and animal studies which studied gender

differences with postoperative pain using an NMDA antagonist. Therefore, we determined that the detected effect size needed to approximate a large effect size.

Using the statistical tool G-Power with alpha (α) set at 0.05, power at 0.80, and an effect size set at 0.35, the minimum number of subjects required for this study was 68. Eight additional subjects were added to account for a possible attrition rate of 10%.

Subjects were stratified into two groups based on gender, then randomly assigned to one of two cells with 19 subjects per cell. Subjects were assigned to one of four cells. Cell I were males who received oral dextromethorphan preoperatively. Cell II were males who received an oral placebo preoperatively. Cell III were females who received oral dextromethorphan preoperatively. Cell IV were females who received an oral placebo preoperatively.

Instrumentation

Data collection was completed as follows. The demographic data collection sheet provided information regarding gender, age, surgical procedure, weight, body mass index, and race. The subject's baseline measurement for preoperative patient perception of pain was recorded on

the demographic data collection sheet (see Appendix B).

Patient perception of pain was assessed using the Numerical Rating Scale (NRS) (see Appendix C). The NRS is an 11-point verbal rating scale with zero being no pain and ten being the worst pain that the patient could perceive. While the NRS is ordinal data, studies have shown a strong correlation (r = .81, p < .01) between the Visual Analogue Scale (VAS) and the NRS (Jensen, Turner, & Romano, 1994; Ohnhaus & Adler, 1975; Woodforde & Merskey, 1972). Jensen, Turner, and Romano (1994) showed a strong correlation for analyzing patient's pain between the VAS and the NRS, where 124 cancer patients were assessed for pain using various pain assessment tools. The NRS was found to be just as reliable as the VAS.

The time from surgical completion to the patient's first request for pain, and the total amount of postoperative pain medication used for the first 24 hours following surgery was recorded on the data collection sheet (see Appendix B).

Procedure for Data Collection

Patients scheduled for arthroscopic knee surgery and meeting inclusion criteria were offered the opportunity to

participate in this study. The purpose, procedures for data collection, and how to rate their pain using the data collection instruments were explained to the patients. When the patient agreed to participate in the study, they were randomly assigned and stratified into a group. Subjects were stratified into one of two groups based on gender to ensure equal distribution of control and study drug subgroups by gender. A faculty member randomly assigned the subject to one of two groups based on a list of random numbers. Group A received a placebo of 15 milliliters (ml) fructose medium while group B received 15 ml of 1.5 milligrams per kilogram (ml/kg) dextromethorphan in a fructose medium. The study participant and anesthesia provider were blinded to which group received the placebo and which group received the dextromethorphan. The medium was ingested by mouth 45 minutes prior to the scheduled start time of the surgery.

A colored folder attached to the chart with all the necessary data collection tools and consent forms therein identified subjects participating in the study. The placebo or medication was attached to the folder in a 15 ml syringe enclosed in a zip lock bag. The researcher reviewed the

consent and the scoring instructions on the data collection instruments before the study subject received the study medication.

Preoperative preparation of the patient was conducted according to the standard operating procedures established by the medical treatment facility (MTF). The patient was assessed for a baseline level of pain using the NRS. An intravenous catheter was secured and maintenance fluid initiated in the pre-op holding area.

The anesthesia provider utilized a standardized anesthesia plan. This plan consisted of preoperative, induction, and maintenance drugs having been standardized. Preoperative drugs were midazolam 1-2 mg IV. For induction anesthesia providers could use fentanyl 1-4 mcg/kg IV, propofol 2-3 mg/kg IV, and a neuromuscular blocker of their own choice. During the maintenance period of anesthesia any desired potent inhalation agent was used. Additionally, the fraction of inspired concentration of oxygen remained greater than thirty percent. Maintenance level of fentanyl was between 1-5 mcg/kg/hr IV, but did not exceed that level. Orthopedic standard of care for knee arthroscopy at this facility required injection of 50 ml 0.25% bupivicaine

with 1:100,000 epinephrine at puncture site. Restrictions were not made on other adjuncts to anesthesia.

Following completion of the surgical procedure and upon arrival to the PACU, the patients were asked to assess their pain based on the NRS. The data were recorded on the colored data collection sheets provided in the folder attached to the patient's record. The patient's pain perception was recorded at 15-minute intervals for the first hour, then at four hours and twenty-four hours post operatively. When a patient was admitted to the hospital, the nursing staff conducted the subsequent data collection. If the patient was discharged prior to the four or twenty-four hour intervals, a take-home data collection sheet with a self addressed stamped envelope was provided to the patient prior to discharge.

Additional data recorded were the time increment from arrival to the PACU until the first request for pain medication. The total amount of pain medication received during the initial twenty-four hour postoperative period was also recorded.

Protection of Human Subjects

This study was approved by the Institutional Review Board at the Medical Treatment Facility (MTF) and from the University of Texas Health Science Center at Houston. All subjects were counseled in the Surgical Services Center the day they had their preoperative counseling and informed consent was obtained. The informed consent included the purpose of the study, potential risks and benefits, how confidentiality is maintained, and how the information gained from the study is reported. As part of the counseling, subjects were informed that they would have access to the results if requested, and that they could withdraw from the study at any time without obligation or fear of being denied further care. (Appendix D).

Confidentiality and anonymity was maintained by assigning a number to the syringe that contained either the placebo or the medication. That number was recorded on the anesthesia record and the data collection tool. A record of the contents of each numbered syringe was kept. This number was also used when entering subject data into the computer for tracking and analysis. The data collection sheets with the demographic data and results were identified only by a

unique patient code. A separate log, which linked the subjects name to their unique identifier, was kept separately from data and informed consents in a double locked file. This link was destroyed after data analysis.

Study Design

This study was a quasi-experimental, double blind, 2x2 randomized block design stratified for gender. Subjects consisted of a convenience sample of patients undergoing arthroscopic knee procedures at a medical treatment facility. These patients were divided into a male and female group to block for gender. Each group was randomly divided into an experimental and control group. Through this gender stratification and randomization there were four groups, both a male and female control and experimental group. Subjects in the control groups received a placebo, which consisted of 15 ml of a fructose solution. Subjects in the experimental group received the study drug, which consisted of 1.5 mg/kg of dextromethorphan suspended in a fructose solution. All subjects received either the placebo or study drug 45 minutes before surgery. In the postoperative period three measurements were recorded. These measurements were: pain perception assessed using the

NRS, the length of time after surgery until the patient required pain medication, and the total amount of pain medication required for pain relief.

Summary

This chapter described the overall methodology of this study. This chapter detailed the population, sample, setting, instrumentation, procedure used for data collection, efforts proposed for the protection of human subjects, and the proposed study design we used to evaluate postoperative pain. This study is a prospective, double blinded, quasi-experimental randomized study, stratified by gender to compare the effects of preemptive oral dextromethorphan on perceived pain in male and female patients undergoing arthroscopic knee procedures.

CHAPTER IV

Analysis of the Data

The purpose of this study was to compare the effect of preemptive oral dextromethophan on perceived postoperative pain in male and female patients undergoing arthroscopic surgery. In this chapter, the investigators discuss data and data analysis including sample characteristics, primary and secondary findings. The investigators used SPSS version 10.0 for Windows to analyze the data.

Sample Characteristics

Sample

The convenience sample of this study was drawn from ASA I, II, and III patients receiving arthroscopic knee procedures at a major military medical center. This sample population was made up of 33 men and 6 women between the ages of 19 and 69, with mean weights between 83.25 and 94.75 kilograms, and body mass index (BMI) between 27.88 and 31 kg/m2.

Forty-six patients were approached to be a part of our study, 42 patients volunteered and 3 were dropped from the study. The attrition rate was 7.14%, which included 3 participants. One participant was dropped from the study

due to change in study procedures, one due to lack of clinical data and one for a surgeon's decision not to follow the established protocol. Thirty-nine participants data was analyzed in this study.

The sample characteristics for the patients who were enrolled in the study are shown in Table 1. There was no statistical difference in the demographics between groups of the four cells.

Primary Findings

This study was designed to determine if there was a difference in perceived postoperative pain between males and females that receive preemptive dextromethorphan.

Hypothesis 1: There is a difference in the level of postoperative pain perceived by females as compared to males who receive preemptive oral dextromethorphan prior to undergoing an arthroscopic procedure.

Using a repeated measures ANOVA tests of between subjects effects with an alpha level of .05, the effect of gender in the experimental group was not statistically significant, $F(1, 15.3) = 2.21$, $p = .16$. The null hypothesis was supported.

Table 1

Subject Characteristics

	N	Mean	Std.Deviation
MALE	33		
Age(yrs)		36.33	13.45
Height(cm)		178.82	6.67
Weight(kg)		91.58	14.47
FEMALE	6		
Age(yrs)		29.67	14.62
Height(cm)		166.67	8.70
Weight(kg)		85.17	25.47

Note: yrs=years, cm=centimeters, kg=kilograms

Hypothesis 2: There is a difference in the level of postoperative pain perceived by females as compared to males undergoing an arthroscopic procedure.

Using a repeated measures ANOVA tests of between subjects a significant difference was found between gender and perceived pain for those who received a placebo. Females perceived greater pain than males, $F(1, 117) = 6.29$, $p = .03$. The null hypothesis was not supported.

Secondary Findings

Perceived pain for patients receiving preemptive dextromethorphan was compared to those receiving a placebo using a repeated measures ANOVA tests of between subjects. No significant difference was found between these groups, $F(1, 20.2) = 1.21$, $p = .28$.

The first request for pain medication was analyzed using a T-test. There was no significant difference between the placebo group and the dextromethorphan group, $F(24, 117) = 5.29$, $p = .20$. When gender was compared for first request for pain medication there was a significant difference with females requesting pain medication sooner than males, $F(29, 68) = 5.24$, $p < .01$.

The total amount of pain medication given

postoperatively for the first 24 hours was analyzed using a T-test. There was no significant difference between the placebo group and the dextromethorphan group, $F(25, 11) = 2.12$, $p = .66$. When gender was compared for total amount of pain medication given postoperatively, no significant difference was found, $F(25, 15) = 0.03$, $p = .33$.

The reported pain over 24 hours was analyzed using the Friedman Test. The Friedman test is the nonparametric equivalent of the one-way within subjects ANOVA. In this study, it was used to rank the scores for each subject across five data collection points. Pain varied significantly across the five assessment points ($\chi^2 = 15.30$, $df = 4$, $p < .01$). Both the dextromethorphan and placebo group reported increasing pain. (see figure 3).

The reported pain and type of arthroscopic procedure was analyzed using a repeated measures ANOVA tests of between subjects. No significant difference was found, $F(1, 18) = 0.10$, $p = .75$.

Figure 3. Bar Graph of mean of NRS pain scores

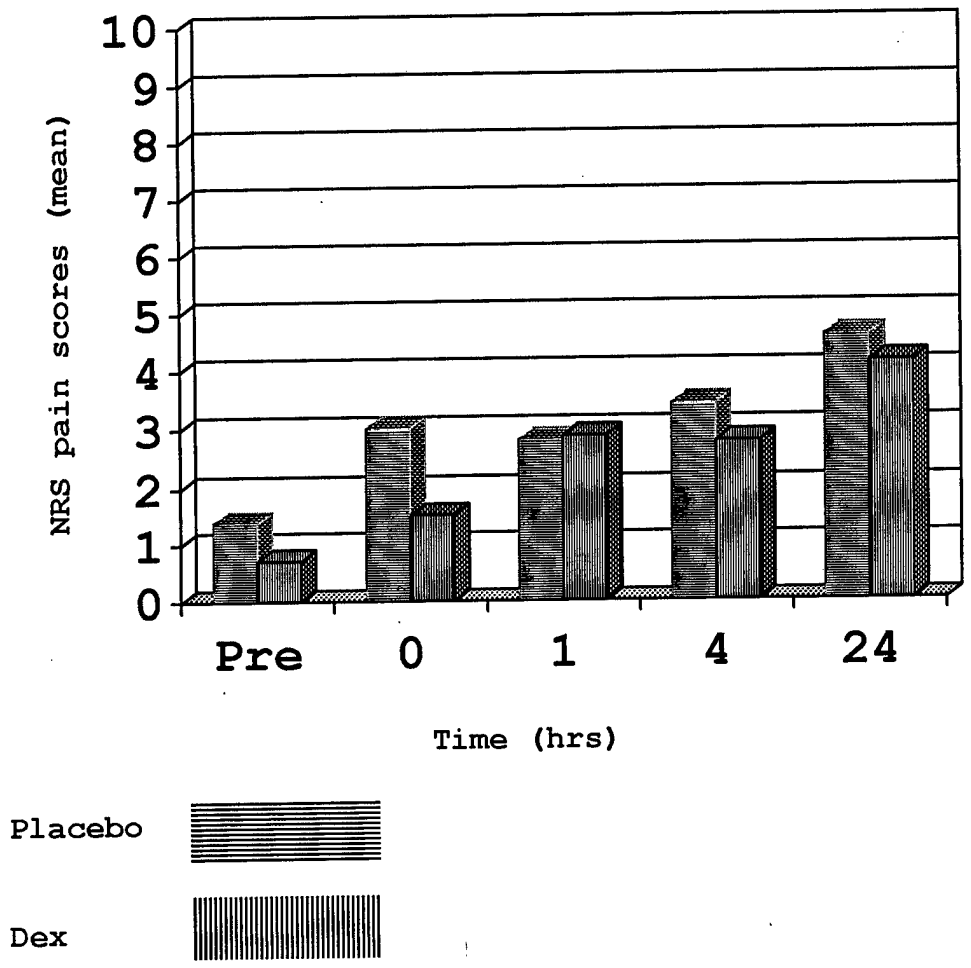


Fig 3. Pre = Baseline pain score, 0 = arrival to PACU, 1 = 1 hour postoperative, 4 = 4 hours postoperative, and 24 = 24 hours postoperative. Dex = dextromethorphan

Summary

There were significant differences found in the placebo group between genders and reported pain. Additionally there was a significant difference between genders for the first request for pain medication.

There were no significant differences between male and female patients perceived pain who receive preemptive dextromethorphan. Additionally there were no significant differences found for total pain medication for the first 24 hours. There was no difference in the type of arthroscopic procedure and the reported postoperative pain.

CHAPTER V

Discussion

Conceptual Framework

One goal of anesthesia providers is to ensure that patients awaken after surgery with minimal pain and to maintain pain control throughout the postoperative period (Penning, 1996). Preemptive analgesia reduces the development of postoperative pain by blocking pain pathways before central sensitization occurs (Melzack, Coderre, Katz, & Vaccarino, 2001). The concept of preemptive analgesia is based on the premise that it is easier to prevent pain rather than titrate medications to reduce pain once it has already been established (Agency for Health Care Policy and Research, 1994). Several mechanisms are responsible for postoperative pain; this allows anesthesia providers to use different drugs for their specific actions to decrease postoperative pain.

Dextromethorphan has been studied extensively for its N-methyl-D-aspartate (NMDA) receptor antagonist properties. Multiple studies in animals and humans concluded that NMDA receptor antagonists were effective in preventing central sensitization and therefore reduced pain perception

following nociceptive stimuli of surgical procedures (Bennett, 2000; Chia, Liu, Chow, & Lee, 1999; Henderson, Withington, Wilson, & Morrison, 1999; Price, Mao, Frenk, & Mayer, 1994; Woolf & Thompson, 1990; Wu et al., 1999). The degree of central sensitization inhibition may be dependent upon gender differences. Presently there are no published human studies that have evaluated gender differences for central sensitization. This study compared the effects of preemptive oral dextromethorphan on perceived postoperative pain differences in male and female patients undergoing arthroscopic knee surgeries.

Primary Findings

The first hypothesis stated that there is a gender difference in the level of postoperative pain perceived for those patients receiving preemptive dextromethorphan. The results of the statistics on this patient population did not support this hypothesis. These results cannot be generalized because the sample size was smaller than required for adequate power. The amount of females required for the female dextromethorphan cell was nineteen, yet only four were enrolled. With the smaller sample, a small effect

is more difficult to detect.

The second hypothesis stated that there is a gender difference in level of postoperative pain perceived for those patients receiving a placebo. A significant difference was found with females reporting a higher level of pain, however the female sample for this cell was only one patient. This patient started with a high pain perception before surgery, rating her pain at baseline of 9/10. A significant difference was calculated between males and females, however, with the female sample size of one, the assumptions and conditions for an ANOVA have not been met. An assumption of an ANOVA is that there is a normal distribution, with a sample size (*n*) of one, a normal distribution could not be generated.

Additional Findings

The NRS was used as the primary instrument with which patients rated their perception of postoperative pain. Additionally, subjects first request for pain medication and total pain medications were used as measures of dependent variables to provide more objective and less subjective information of the patients postoperative pain.

A significant difference for first request for pain medication between males and females was shown. Females had a mean time to first request for pain medication of 12.20 minutes (SD = 15.59), while men had a mean time of 215.52 minutes (SD = 366.58), F = 5.24, df = 28.56, p = .01. Female patients that received a placebo had a mean time of 13.00 minutes (SD = 16.97) and the males had a mean time of 121.13 minutes (SD = 238.18), F = 1.273, df = 14.78, p = .11. Female patients that received dextromethorphan had a mean time of 11.67 minutes (SD = 18.47), while men had a mean time of 316.64 minutes (SD = 455.03), F = 4.861, df = 13.19, p = .026.

This data showed that females ask for pain medications sooner than do male patients in our study population. Any comparison of gender in this study is difficult due to the small number of female subjects enrolled and the initial high level of perceived pain.

The subjects perceived pain scores increased over the twenty-four hour period with the exception of the dextromethorphan group at the four-hour data point. It is unknown why there is a decrease in reported pain at the

four-hour interval. The increase in pain may be due to the effect of the local anesthetic diminishing, which was injected on wound closure per the standard anesthetic plan. It is difficult to interpret this finding because of this confounding variable.

Study Strengths

While this study was unable to achieve the required sample size, there were several strengths of the study. The data collection tool was easy to understand by both the staff and patients and made it easy to collect the necessary data. Patients' comments from the home questionnaires returned stated that they had a positive surgical experience and their pain control was manageable. The actual attrition rate of 7% was less than the predicted rate of 10%. The placebo and the drug were indistinguishable from each other by taste. Previous studies had difficulty in disguising the taste of oral dextromethorphan from the placebo, which weakened the double blinding of the study.

Study Weaknesses

A critical review of our clinical research was

conducted upon completion of data collection. This revealed study weaknesses; to include use of local anesthetics, short time frame, change in patient population, and the use of two different surgeries to attain a sample.

The medical facility in which this study was conducted used a standard of care for arthroscopic knee procedures that included injecting local anesthetic into the wound pre-incision and at the time of wound closure. This practice introduced a confounding variable into the study that may have interfered with the ability to obtain a clear understanding of the relationship of pain over time and hindered the ability to interpret the findings. As a result we were unable to gain a true evaluation of the effectiveness of dextromethorphan.

The time frame allotted for this study, due to the limits of our academic requirements, limited our ability to attain the required sample size in both number and gender. The study had several challenges to face which left only a five month time frame to collect patient data. The challenges were to obtain IRB approval at two institutions,

changing patient populations because of a competing study for our initial approved population, seeking a waiver for off label use of dextromethorphan, and enrolling equivalent number of men and women to analyze a difference in gender. The limits of time prevented our ability to adequately attain an equivalent number of men to women for comparison. As a result far more men than women were recruited. Given more time we may have been allowed to enroll the required sample size of women.

During the course of the study, the initial targeted patient population had to be changed after initial IRB approval. The study was conceptualized initially to analyze gender differences in laparoscopic procedures for general surgery patients, however a competing study for the same patient population which was already in progress at the time of IRB approval did not finish its requirements on time. This competing study made the originally chosen population unavailable to our research. Therefore an arthroscopic patient population was chosen in an attempt to attain equal gender participation.

Another weakness was using two separate surgeries to

attain a sample population. Surgical candidates presenting for arthroscopic knee surgeries that consisted of either knee arthroscopy or ACL repair were used. Although the statistics revealed no statistical differences for pain in these surgeries, there are differences between these surgeries, which may introduce more variables making it more difficult to control extraneous variables. The length of time is statistically significant between these procedures ($p < .01$), with a mean for the knee scope of 61.04 minutes, and arthroscopic ACL repair mean of 159.62 minutes. While addressing the study weaknesses, threats to internal validity and external validity were noted.

Internal Validity

The threats to internal validity included history, selection bias, maturation, testing, instrumentation, and mortality. History was a threat to the internal validity of this study. We randomly assigned patients to the experimental or control groups to minimize this threat. However, during the study our potential patient population was deployed to Operation Iraqi Freedom. This may have affected our ability to enroll other potential candidates

that were both male and female soldiers serving our country.

Selection bias was a threat to the internal validity of this study. During the enrollment, it was not possible to randomly select subjects from the population; therefore a convenience sample was used, which introduced additional threats to the internal validity. This threat was minimized by randomly assigning subjects to either a control or experimental group to avoid nonequivalence of the groups. However, we were unable to attain enough women to have equivalence for either the placebo or control group.

The threats of maturation, testing, and instrumentation were minimal. The study was short, encompassing approximately twenty-four hours time for most study participants. The tool used for testing was the NRS, which standardized the testing and the instrumentation threats to internal validity. The NRS required the patient to verbally rate his/her pain according to a scale from zero to ten. Since this instrument did not require a rater, inter-rater reliability was not an issue. However, the instrumentation threat may exist at the data point where

the subjects arrived in the PACU if the patients were too sleepy to understand how to rate their pain level from zero to ten.

Mortality was a threat to this study. Twelve participants did not return questionnaires, or they were lost in the delivery process. Phone calls were made at the twenty-four hour data collection point, but only if the participants were not in hospital already. One patient was discharged home with the data collection tool, making it impossible to recapture this data.

External Validity

A threat to external validity of this study also included the selection of this sample population. Since the sample population is not randomly selected it will be difficult to generalize these findings to other patient populations.

Another threat to the external validity of this study was the Hawthorne effect and novelty effect. The study controlled for this threat by using a placebo medication, however, it is unknown if the patients responded any differently because they were comparing themselves to the

opposite gender, for example, "Who really is the stronger gender, I will show them."

Conclusions

Even though this study was unable to generalize its findings to a broader population, significance was shown between the genders in first request for pain medication and in pain perception. The findings of this study, however, must be viewed with caution because of the inability to recruit the required sample size. The significance that was detected involved a small sample size. Additionally the introduction of confounding variables may have interfered with the findings. Gender differences for pain with the use of preemptive dextromethorphan remains unanswered.

Implications and Recommendations for Further Research

Further research that attempts to duplicate our study should consider the use of dextromethorphan in multiple administrations. It is possible that dextromethorphan did not block enough receptors or that a one time dose does not block receptors long enough to decrease central sensitization. It is our recommendation that the study be

duplicated where dextromethorphan be administered 8 hours prior to surgery, 45 minutes prior to surgery, and 8 hours after surgery. By administering dextromethorphan with this time schedule, both of the above hypotheses could be tested.

This study was unable to reach the required sample size, therefore significantly more male than female subjects were recruited. It is recommended that further studies looking at gender differences with the use of dextromethorphan as preemptive analgesia select a patient population that will have equal distribution of males and females. A multi-center study would improve the ability to recruit required numbers of male and female subjects.

This study indicated an increase in pain at twenty-four hours. Based on this finding, another recommendation for further research may include a separate study on whether patients are being adequately controlled for their pain at the twenty-four hour time period.

It was noted that when a study subject received a twenty-four hour callback the home questionnaire form was more likely to be returned. It is our recommendation that

one person be assigned to follow up with the study subjects when doing the twenty-four hour callback. When more than one person was involved with collecting data, some data collection information was missed. Assumptions were made that twenty-four hour callbacks were initiated when they were not. Electronic charting helped to capture the missing data points. However, this capability may not always be available. Hence, the main reason for having the twenty-four hour callback to the study subjects was to insure that data was collected in case the subject did not send back the home questionnaire. It cannot be stressed enough the importance of following through with the twenty-four hour callbacks.

Future clinical studies involving gender differences and perceived pain may be necessary to achieve adequate postoperative pain control. The use of NMDA antagonists may be a strong link to decreasing patients' postoperative pain. Research that can answer the question whether or not gender differences have an affect on perceived pain will assist the anesthesia provider in decreasing patient pain and increase patient satisfaction.

APPENDIX A

Letter of Approval from COL Norma Garrett

To CPT Jim Eads

Subject: Approval to use diagrams from AANA Journal

I consider it an honor that you would find the diagrams in my paper useful. Please use them as you need. Good luck. I hope this e-mail will suffice.

COL Garrett.

APPENDIX B

Demographic/Data Collection Worksheet

Data Collection Worksheet

Preoperative Data

Patient ID # _____

Date of Surgery_____

Arthroscopic procedure_____

Demographic/Preoperative Data

Age: _____ Height: _____ (cm) Weight: _____ (kg) BMI: _____

Gender:_____ ASA: _____ Ethnicity: _____

Numeric rating Scale: (to include location of pain)

Preoperative: _____ Location: _____ Time: _____

Time given DM/Placebo: _____

Intraoperative Data

Time of laryngoscopy: _____ Estimated time since DM/Placebo: _____ (min)

Time of first incision: _____

Time of surgery completion:_____

Duration of Surgery: _____ (min)

Local anesthetic used?: Yes No Type: _____ Amount: _____(mg)

Postoperative Data

PACU arrival time: _____ Discharge time: _____

Time of first administration of postoperative medication: _____

Nausea: YES NO Time: _____

Emesis: YES NO Time: _____

Antiemetics received: Type: _____ Amount: _____ Time: _____

Total dose & type of postoperative analgesic administration

_____

Admitted?: YES NO If yes, why?

_____

Numerical Rating Scale scores and location of reported pain

Time **Pain Score**

_____ Immediately on arrival to PACU _____Location_____

_____ 1 hour postop, or discharge from PACU_____Location_____

_____ 4 hours postop, or discharge from PACU_____Location_____

_____ 24 hours postop _____ Location_____

Time of discharge from hospital: _____

"Take home" questionnaire returned? YES NO

Return phone call comments:

_____

_____

_____

APPENDIX C

Home Questionnaire

Home Questionnaire

Thank you for agreeing to participate in our study. We wish you a speedy recovery and will be calling you at some time 24 hours after your surgery to see how you are doing. Please take time to fill out this questionnaire prior to us calling you. Whether we are able to contact you or not, please mail this completed form back to us within 2-3 days with the self-addressed and stamped envelope provided. Thank you again for participating in our study. Your participation may help other patients like you in the future, by helping us to understand the differences in pain perception between men and women.

Using the table below please record the amount of pain you were having at the indicated times using the same pain scale you used in the hospital. 0 being no pain and 10 being the worst pain you can imagine. Also please enter the type and number of pain medications you took for that time period.

Date/Time	Amount of Pain	Where Is Your Pain Felt
Date: Time:	Score:	
Date: Time:	Score:	
Date: Time:	Score:	

Please Record the date and times for any pain medications on the reverse of this form

Date and Time	Medication Name	Number of Pills Taken

In addition to the above, please take the time to answer the following questions.

1. Are there any other methods that you used to relieve your pain after surgery (prayer, hot/cold packs, position in bed, meditation, etc.)? _____

_____

_____.

2. Did you have any nausea after leaving the hospital? YES NO

3. Did you vomit after leaving the hospital? YES NO

4. Would you like a copy of the results? YES NO

If yes please provide your address (We anticipate results will be available around Nov. 2003)

From *The effect of pre-emptive Administration of dextromethorphan on postoperative pain in patients undergoing interval laparoscopic tubal sterilization.* by B. M. Pitcher, 2001. Unpublished masters thesis, University of Texas Health Science Center at Houston. Adapted with permission of the author.

APPENDIX D

Informed Consent

VOLUNTEER AGREEMENT AFFIDAVIT

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

PRIVACY ACT OF 1974

Authority: 10 USC 3013, 44 USC 3101 and 10 USC 1071-1087

Principle Purpose: To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purpose.

Routine Uses: The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs, teaching, adjudication of claims, and for the mandatory reporting of medical condition as required by law. Information may be furnished to Federal, State and local agencies.

Disclosure: The furnishing of SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

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

I, _____ SSN _____ having full capacity to consent and having attained my _____ birthday, do hereby volunteer to participate in the research protocol ``**A Comparison of the Effects of Preemptive Oral Dextromethorphan on Perceived Postoperative Pain in Male and Female Patients Undergoing Arthroscopic Knee Surgery**'' under the direction of **CPT Brent J. Persons, AN**, conducted at Madigan Army Medical Center.

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

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. **Should any further questions arise concerning my rights study-related injury I may contact the Center Judge Advocate at Madigan Army Medical Center, (253) 968-3113.**

I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits; however, I may be required (military volunteer) or requested (civilian volunteer) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary 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 - EXPLANATION OF WHAT IS TO BE DONE

INTRODUCTION: You have been invited to take part in a clinical research study called ``A Comparison of the Effects of Preemptive Oral Dextromethorphan on Perceived Postoperative Pain in Male and Female Arthroscopic Knee Surgery'', conducted at Madigan Army Medical Center because you are having laparoscopic surgery. Taking part is entirely voluntary; if you decide not to take part, penalty or loss of benefits to which you are otherwise entitled will not be effected. A total of 76 patients will be enrolled in the study at Madigan Army Medical Center.

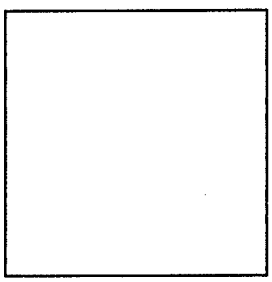
PURPOSE: The purpose of the study is to determine if there is a difference between men and women in pain perception after they have been given a drug to relieve pain

before surgery and those who have not been given a drug before surgery.

EXPLANATION: Studies have shown that preemptive analgesia (pain medication given before surgery) may decrease pain after surgery. Preemptive analgesia is the term used for giving pain medication before a painful event, such as surgery, to decrease the amount of pain a person feels after the event. The drug used in this study for preemptive analgesia is called dextromethorphan. Dextromethorphan is a drug that has been studied for preemptive analgesia and shown to reduce pain after surgery. Other recent studies have also shown men and women feel pain differently, and men and women do not have the same effect from some pain medications. This study will compare the differences between how men and women feel pain after surgery when they have been given preemptive analgesia to see if their pain should be managed differently. To help treat pain after surgery as best as possible, it is important for health care providers to understand if there is a difference in how men and women feel pain after surgery when they have been given the study drug before surgery.

PROCEDURES: If you agree to participate in this study, you will be randomly assigned in one of two groups to receive the study drug. Randomization, such as a flip of a coin, makes sure that every one has an equal chance of being selected to receive the study drug. One group will receive dextromethorphan 1.5 mg per kilogram of body weight (about 3 teaspoons of surgary syrup) by mouth and the other group will receive a placebo. In this study, the placebo is an a fructose syrup that looks like dextromethorphan but has no know side effects. Neither you nor your anesthetist will know which one you will get.

On the day of surgery, after your intravenous (IV) catheter has been started by the staff, we will ask you to rate your pain on a pain survey that uses a scale of zero (0) to ten (10). Zero means absolutely no pain and ten means the worst pain you can imagine. After this you will be given the study drug to drink. When you awake in the recovery room, you will be asked by your nurse to rate your pain again using the same pain survey. If you stay in the hospital for the next 24 hours, you will asked to rate your pain three more times. If you go home before the 24 hours, the pain survey will be sent with you and you will be asked to record your pain scores at 4 and 24



hours after you arrived in the recovery room. An investigator will either visit you in your hospital room or call you at home the day after surgery to answer any questions or assist you with the survey.

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

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

RISKS, INCONVENIENCES, AND DISCOMFORTS: Dextromethoraphan is the same medication found in cough syrup. Side effects can occur **in large amounts beyond what you will receive** in this study (300mg or more). They include: nausea, vomiting, constipation, feeling `high', restlessness, hallucinations, skin reactions. You may or may not have a decrease in pain after surgery. Additionally, filling out the pain survey will require about 5-10 minutes of your time.

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

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

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

CONFIDENTIALITY OF RECORDS: The case records from this study will be available for review by members of the Institutional Review Board at Madigan Army Medical Center, the Institutional Review Board at the University of Texas-Houston Health Science Center, representatives of the Food

and Drug Administration (FDA), and other governmental agencies as part of their normal duties. All records will be kept in a confidential manner. Otherwise, only the individuals conducting this study will have access to the records from this study. Information gained from this study may be used as part of a scientific publication, but you will in no way be personally identified. Complete confidentiality cannot be promised, particularly for military personnel because information bearing on your health may be required to be reported to appropriate medical or Command authority.

OTHER INFORMATION: Significant findings that occur during this study that might affect your decision to participate in the study will be discussed with you. Any significant findings developed from this study will be available to you and may be obtained from your physician. Your participation in this study may be terminated without your consent if conditions occur which might make your continued participation dangerous or detrimental to your health; or if military contingency requires it; or if you become ineligible for military care as authorized by Army regulation.

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

You are encouraged to ask any questions, at any time, that will help you to understand how this study will be performed and/or how it will affect you. You may contact CPT Brent Persons at (253) 241-4421.

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

This study (HSC-SN-02-039) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) for the University of Texas Houston Health Science Center. For any questions regarding research subect's rights, or to report any research related injury, call the CPJS at (713)500-5827.

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

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

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

APPENDIX E

Letter of approval from MAJ Brian Pitcher

TO: CPT Jim Eads

FROM: MAJOR Brian Pitcher

RE: Letter of Approval

This letter is hereby written to give permission for CPT Jim Eads, CPT Mark Grieves, CPT Brand Peck, and CPT Brent Persons to use and adapt the data collection tool that appears in my thesis.

SINCERELY,

MAJOR Brian Pitcher

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VITAE

Brent Persons was born in Greeley, Colorado on June 22, 1966, the son of Roger and Betty Persons. After graduating from Central High School in Greeley, Colorado, in 1984, he enlisted in the United States Army in 1985. As a Staff Sergeant he was accepted for a Green to Gold scholarship and attended the University of Colorado at Colorado Springs in 1991. In 1992, he began perusing a degree in nursing through Beth-El College of Nursing and obtained a Bachelor of Science in Nursing in May 1995. His first duty assignment as a commissioned officer was at Madigan Army Medical Center (MAMC) located at Fort Lewis, Washington. There he worked in the Emergency Department for two years followed by a six-month assignment to Honduras. After returning to MAMC, he was assigned to the Post Anesthesia Care Unit and worked there until his next duty assignment at Fort Carson, Colorado in 1998. While at Evans Army Community Hospital in Fort Carson, Colorado, he was the Assistant Head Nurse for the medical/surgical ward, Director for Troop Medical Services, and Assistant Head

Nurse for the Emergency Department. In 2001, he was accepted into the U.S. Army Graduate Program in Anesthesia Nursing. He has completed phase I of the program and is anticipating completion of phase II at MAMC to earn the degree of Master of Science in Nursing.

James Eads was born in Jerseyville, Illinois on March 18, 1966, the son of Keith Eads and Nellie Barrett. After graduating from Jersey Community High School, Jerseyville, Illinois, in 1984, he entered Southern Illinois University-Carbondale in Carbondale, Illinois. He later attended Trinity Bible College in Ellendale, North Dakota and Rhema Bible College in Tulsa, Oklahoma. In 1988, he attended Army Basic Training and Advanced Infantry Training at Fort Benning, Georgia. After graduating from Advanced Individual Training in December 1988, he was assigned to HHC 1/327th Infantry at Fort Campbell, Kentucky where he served as an advance scout in the scout platoon. In March 1990, he was assigned overseas to South Korea where he was a Sniper team leader with HHC 1/506th scout platoon while stationed on the demilitarized zone. In April 1991, he was assigned to Fort Ord, California where he was a squad leader with C company

1/9th Infantry. In May, 1992, he was honorably discharged from the US Army. In August 1992, he entered the Associate Degree program for Registered Nursing at Lewis & Clark Community College in Godfrey, Illinois and graduated in December 1994. After passing the licensure exam in February 1995, he accepted a position in the OR department at Memorial Medical Center in Springfield, Illinois. In May 1995, he received a reserve commission in the Army Nurse Corps and was assigned to the State Medical Detachment in the Illinois National Guard. In February 1997, he accepted a position in the open-heart surgical services at Memorial Hospital in Belleville, Illinois. In May 1998, he married Rhonda Jane Jenkins. In August 1998, he transferred to the medical-surgical intensive care unit. In May 1999, his son Alexander Ryan Eads was born. In December 1999, he completed his Bachelor of Science in Nursing (BSN) at McKendree College in Lebanon, Illinois. In March 2001, he entered active duty in the U.S. Army and completed the officer advance course. In May 2001, his daughter Abigail Anne Eads was born. In June 2001, he entered the US Army Graduate Program in Anesthesia Nursing, affiliated with

University of Texas Houston Health Science Center. He has completed phase I of the U.S. Army Graduate Program in Anesthesia Nursing, and pursuing completion of phase II at Madigan Army Medical Center, at Fort Lewis, Washington to earn the degree of Master of Science in Nursing.

Mark Grieves was born in Warren, Michigan on June 5, 1973, the son of Millie Rose Grieves and Warren Alfred Grieves Jr. After graduating from Perry High School, Massillon, Ohio, in 1991, he entered Creighton University School of Nursing, in Omaha, Nebraska. During the summer of 1992, he attended Walsh College, in Canton, Ohio. The following summer he attended Omaha Metropolitan Community College, in Omaha, Nebraska. The summer of 1994 he attended US Army Reserve Officer Training Corps Advanced Camp, with a nurse summer training program at Walter Reed Army Medical Center, in Washington, D.C. He graduated Magna Cum Laude from Creighton University conferred with the degree of Bachelor of Science in Nursing (BSN) in May 1995. During the following two years, he was employed as the head nurse of Creighton University Diabetes Research Center, Omaha,

Nebraska. In 1997, he entered active duty in the US Army Nurse Corps, and worked as a medical-surgical nurse from 1997-1999 at Madigan Army Medical Center, at Fort Lewis, Washington. He then became a post-anesthesia care unit nurse, and worked as such from 1999-2001. In February 2000, his daughter Emily Rose Grieves was born. In June 2001, he entered the U.S. Army Graduate Program in Anesthesia Nursing, affiliated with University of Texas Houston Health Science Center. He has completed phase I of the U.S. Army Graduate Program in Anesthesia Nursing, and pursuing completion of phase II at Madigan Army Medical Center, at Fort Lewis, Washington to earn the degree of Master of Science in Nursing.

Brandi Peck was born in Homer, Alaska on June 8, 1973, the daughter of David and Marti Anderson. After graduating from Homer High School in Homer, Alaska, in 1991, she enrolled at Penn State University. In 1993, she was married to Trenton Peck from Bozeman Montana. She transferred to Montana State University to pursue a degree in nursing and obtained a Bachelor of Science in Nursing May 1997. Her first duty assignment was at HMEDDAC in Heidelberg, Germany in the newborn nursery. In 1998 she began working as a

labor and delivery nurse on the mother baby unit. In 2000, she moved to the post anesthesia unit to fulfill an opportunity as the head nurse of this unit. In 2001, she was accepted into the U.S. Army Graduate Program in Anesthesia Nursing. She has completed phase I of the program and is anticipating completion of phase II at MAMC to earn a Master of Science in Nursing.