REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2002	Final Report (February 2002 - January 2003)

4. TITLE AND SUBTITLE
A comparison of preemptive administration of ibuprofen rofecoxib, and placebo in the attenuation of postoperative pain following gynecological surgery

5. FUNDING NUMBERS

6. AUTHOR(S)
CPT Elizabeth K. Pulatie, CPT Timothy S. Adams, CPT Richard W. Breeding, CPT Timothy J. Bryant, CPT Jason N. Ernest, CPT Steven A. Kindle, CPT Hector Muniz

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Texas Health Science Center at Houston
School of Nursing
P.O. Box 20036
Houston, TX 77225

8. PERFORMING ORGANIZATION REPORT NUMBER
HSC-SN-02-005

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
US Army Medical Department Center and School
BLDG 2840 MCCS-HNE
2250 Stanley Road Suite 214
Fort Sam Houston, TX 78234

10. SPONSORING / MONITORING AGENCY REPORT NUMBER
NA-2002-02

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; Distribution is unlimited

13. ABSTRACT *(Maximum 200 words)*
One of the chief complaints of patients undergoing surgical procedures continues to be postoperative pain, which leads to increased morbidity and mortality. Preemptive analgesia is inhibition of pain pathways prior to a painful stimulus. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be beneficial as preemptive analgesic agents, reducing postoperative pain. The aim of this study was to determine if the preoperative administration of an NSAID reduces postoperative pain and if there was a difference between a non-selective cyclooxygenase (COX) inhibitor, such as ibuprofen, and a selective COX-2 inhibitor, such as rofecoxib. This study was a randomly assigned, double-blinded, placebo-controlled, clinical trail. Patients scheduled for gynecological surgery involving a lower abdominal incision were recruited. Each participant was assigned to one of three treatment groups: ibuprofen 400 mg, rofecoxib 50 mg, or placebo, given orally 1 hour prior to surgery. Pain scores and morphine consumption were the dependent variables measured. Data was analyzed for 36 subjects. No significant differences were found between groups in regard to demographics and the incidence of nausea and vomiting. Although there was not a statistically significant difference, the rofecoxib group had slightly lower Post Anesthesia Care Unit (PACU) admit pain scores (mean 3.50, SD 0.83) as compared to ibuprofen (4.09, 2.59) and placebo (4.09, 3.18). In addition, PACU discharge pain scores were also slightly lower for the rofecoxib group (3.29, 1.98) as compared to ibuprofen (3.45, 1.81) and placebo (3.82, 1.17). Total milligram morphine use was also slightly lower in the rofecoxib group (56.08 mg, 30.11) as compared to ibuprofen (65.90 mg, 42.53) and placebo (69.35 mg, 40.66). Due to time and enrollment constraints, fewer patients were enrolled than required by the initial power analysis. As a result, this study was converted to a pilot study. Participants were limited to patients that were eligible for care at a military treatment facility. Therefore, generalizations to other populations would require additional studies. The study continues to be ongoing at Triple Army Medical Center.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Gynecologic Surgical Procedures, Postoperative Analgesics, NSAIDs (Nonsteroidal anti inflammatory drugs)	123
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

A COMPARISON OF PREEMPTIVE ADMINISTRATION OF IBUPROFEN, ROFECOXIB, AND PLACEBO IN THE ATTENUATION OF POSTOPERATIVE PAIN FOLLOWING GYNECOLOGICAL SURGERY

By

CPT Elizabeth K. Pulatie, AN

CPT Timothy S. Adams, AN

CPT Richard W. Breeding, AN

CPT Timothy J. Bryant, AN

CPT Jason N. Ernest, AN

CPT Steven A. Kindle, AN

CPT Hector Muniz, AN

A Thesis

submitted in partial fulfillment of the requirements for the degree of

Master of Science in Nursing

The University of Texas Health Science Center at Houston

School of Nursing

October, 2002

ABSTRACT

One of the chief complaints of patients undergoing surgical procedures continues to be postoperative pain, which leads to increased morbidity and mortality. Preemptive analgesia is inhibition of pain pathways prior to a painful stimulus. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be beneficial as preemptive analgesic agents, reducing postoperative pain. The aim of this study was to determine if the preoperative administration of an NSAID reduces postoperative pain and if there was a difference between a non-selective cyclooxygenase (COX) inhibitor, such as ibuprofen, and a selective COX-2 inhibitor, such as rofecoxib.

This study was a randomly assigned, double-blinded, placebo-controlled, clinical trial. Patients scheduled for gynecological surgery involving a lower abdominal incision were recruited. Each participant was assigned to one of three treatment groups: ibuprofen 400 mg, rofecoxib 50 mg, or placebo, given orally 1 hour prior to surgery. Pain scores and morphine consumption were the dependent variables measured.

Data was analyzed for 36 subjects. No significant differences were found between groups in regards to demographics and the incidence of nausea and vomiting. Although there was not a statistically significant difference, the rofecoxib group had slightly lower Post Anesthesia Care Unit (PACU) admit pain scores (mean 3.50, SD 0.83) as compared to ibuprofen (4.09, 2.59) and placebo (4.09, 3.18). In addition, PACU discharge pain scores were also slightly lower for the rofecoxib group (3.29, 1.98) as compared to ibuprofen (3.45, 1.81) and placebo (3.82, 1.17). Total milligram morphine use was also

slightly lower in the rofecoxib group (56.08 mg, 30.11) as compared to ibuprofen (65.90 mg, 42.53) and placebo (69.35 mg, 40.66).

Due to time and enrollment constraints, fewer patients were enrolled than required by the initial power analysis. As a result, this study was converted to a pilot study. Participants were limited to patients that were eligible for care at a military treatment facility. Therefore, generalizations to other populations would require additional studies. The study continues to be ongoing at Tripler Army Medical Center.

TABLE OF CONTENTS

CPHS APPROVAL LETTER

THE UNIVERSITY of TEXAS
HEALTH SCIENCE CENTER AT HOUSTON

THE COMMITTEE for the PROTECTION of HUMAN SUBJECTS
322 Jesse Jones Library Building
P.O. Box 20036
Houston, Texas 77225
Cynthia.L.Edmonds@uth.tmc.edu
713 500 5827
713 500 5830 fax

NOTICE OF APPROVAL TO BEGIN RESEARCH February 15, 2002

HSC-SN-02-005 – "A Comparison of Preemptive Administration of Ibuprofen, Rofecoxib, and Placebo in Attenuation of Postoperative Pain following Gynecological Surgery"
P.I.: Elizabeth Pulatie, MSN Student; Timothy Adams, Richard Breeding, Timothy Bryant, Jason Ernest, Steven Kindle, Hector Muniz – MSN Students

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

APPROVED: At a Convened Meeting

APPROVAL DATE: February 15, 2002 **EXPIRATION DATE:** January 31, 2003

CHAIRPERSON: Anne Dougherty, MD 2/19/02

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

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

INFORMED CONSENT – Informed consent must be obtained by the P.I. or designee using the format and procedures approved by the CPHS. The P.I. must instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document.

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

RECORDS – The P.I. will maintain adequate records, including signed consent documents if required, in a manner which ensures confidentiality.

A COMPARISON OF PREEMPTIVE ADMINISTRATION OF IBUPROFEN, ROFECOXIB, AND PLACEBO IN THE ATTENUATION OF POSTOPERATIVE PAIN FOLLOWING GYNECOLOGICAL SURGERY

By

CPT Elizabeth K. Pulatie, AN

CPT Timothy S. Adams, AN

CPT Richard W. Breeding, AN

CPT Timothy J. Bryant, AN

CPT Jason N. Ernest, AN

CPT Steven A. Kindle, AN

CPT Hector Muniz, AN

APPROVED

LTC Bruce Schoneboom, AN

Patricia Nishimoto, DNS

COL Catherine Schempp, AN

MAJ Randy McDonald, AN

MAJ Amy Asato, MC

ACKNOWLEDGEMENTS

We acknowledge and wish to express our sincerest appreciation to our thesis committee and program faculty, Lieutenant Colonel Bruce Schoneboom, Dr. Patricia Nishimoto, Colonel Catherine Schempp, Major Randy McDonald, and Dr. Amy Asato for their wisdom, guidance, and assistance. We acknowledge and appreciate the efforts of Captain Mike Swindle, BSN, for his contributions in the review of the literature and the initial preparations for our first three chapters.

In addition, we wish to acknowledge and thank the anesthesia providers at Tripler Army Medical Center, who assisted us with enthusiasm throughout the entire process to include recruitment of patients, administration of our anesthetic plan, and data collection during the intraoperative period. We also thank the obstetric/gynecologic (OB/GYN) residents and staff physicians for their support and adherence to the study protocol. In addition, we extend thanks to the nursing staff in the PACU, Surgical Admissions Center (SAC), and ward 5B1, for their assistance with data collection.

We also acknowledge and appreciate the assistance of Dr. Catherine Uyehara. Her expertise in data analysis was priceless. Despite her busy schedule, she always managed to fit us in. In addition, Colonel Dennis Beaudoin, Dr. Edwin Goo, and Dr. Blain Yoshinobu from the pharmacy were instrumental in the liquid formulation of rofecoxib, ibuprofen, and placebo. Their efforts in the pharmacy made this study possible.

Finally, we wish to thank our families and our friends for their immeasurable support, patience, and encouragement during this endeavor.

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

Introduction

Reducing postoperative pain and recovery time are two major goals of healthcare providers. Managed care and technological advances are pressing the medical community to reduce hospital stays, increase patient satisfaction, and decrease the overall cost of procedures. Much research has been performed using nonsteroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis and preoperatively to aid in the reduction of postoperative pain and opioid use. Traditional NSAIDs are non-selective cyclooxygenase inhibitors. However, little research has been done comparing preemptive administration of a non-selective COX inhibitor (ibuprofen) to a specific COX-2 inhibitor (rofecoxib) for patients having gynecological surgeries involving incisions of the lower abdominal wall. Surgeries that may involve an abdominal incision include total abdominal hysterectomy (TAH), exploratory laparotomy, myomectomy, microscopic tubal anastamosis (MTA), and cystectomy.

Most of the patients in this study (58.3%) underwent a total abdominal hysterectomy (TAH). A TAH involves a pfannenstiel or midline incision and spreading of the rectus abdominus muscles, through which the uterus, ovaries, and cervix are removed (Margolis, Heinrichs, & Ratner, 1999). Hysterectomy is the second most commonly performed surgical procedure in the United States, approximating 600,000 annually (Falcone, Fidela, Paraiso, Mascha, & Edward, 1999). It is estimated that a third of women will have undergone a hysterectomy by the age of 65 years. Seventy percent of all hysterectomies are performed via the abdominal route (Falcone et al., 1999). The

prevalence of this procedure has brought concern upon for of hospital stay and overall cost. The average postoperative pain scores for TAH patients are 5-8 per the 11-point numerical rating scale (NRS) (Margolis et al., 1999). Many other gynecological surgeries involve a pfannenstiel incision including myomectomy, ovarian cystectomy, abdominal colpopexy, moschowitz enterocele repair, presacral neurectomy, urethropexy, and oophorectomy. In addition, the average postoperative pain scores for these procedures are 5-8 (Sayed, Gibson, Edraki, Holbrook, & Cohen, 1999). Frequent complications of these procedures are infection, pain, nausea, vomiting, and anemia. The purpose of this study supports the medical community's intention to decrease postoperative pain and reduce the length of hospital stays.

Inhibition of COX-1 is thought to account for the platelet dysfunction and adverse gastrointestinal and renal effects of traditional NSAIDs, whereas COX-2 inhibition produces anti-inflammatory effects (Thompson, Sharpe, Kiani, & Owen-Smith, 2000). NSAIDs can be either selective (rofecoxib, celecoxib and valdecoxib) or non-selective (ibuprofen and naproxen) COX inhibitors. The benefits of rofecoxib, a selective COX-2 inhibitor, include postoperative pain reduction with attenuation of the adverse effects associated with the use of non-selective NSAIDs.

The concept of blocking pain pathways prior to surgical incision is known as preemptive analgesia. It is believed that by blocking the chemical mediators responsible for peripheral pain and inflammation, NSAIDs can reduce the phenomenon called wind-up and thereby reduce postoperative pain. This study was based on the concept of preemptive analgesia comparing the non-selective COX inhibitor ibuprofen and the

selective COX-2 inhibitor rofecoxib. Rofecoxib 50 mg was compared to ibuprofen 400 mg and a placebo. Rofecoxib has a clinical efficacy comparable with ibuprofen (Day et al., 2000). Efficacy is the ability of a drug to produce the desired effect, regardless of potency. Potency is the dosage of a drug necessary to achieve the desired effect (Dorland, 2000). Attenuation of the pain-induced stress response, and therefore wind-up, may have the potential to decrease morbidity and mortality, increase patient satisfaction, decrease hospitalization, and reduce the overall cost of the procedure.

Statement of the Problem

Postoperative pain continues to be an ongoing medical concern. The Joint Commission and Accreditation of Health Care Organizations (JCAHO) has mandated hospitals and health care providers to search for effective strategies to treat this problem. Uncontrolled postoperative pain leads to increased morbidity and mortality. This further leads to increased hospital stay and costs, as well as decreased patient satisfaction.

Significance of the Problem

Reducing postoperative pain and untoward effects continue to be a challenge to health care providers. Little research has been performed on preemptive analgesia associated with gynecological surgeries involving lower abdominal incisions. Uncontrolled postoperative pain continued to be a leading cause of unplanned hospital admissions at Tripler Army Medical Center (TAMC). The administration of rofecoxib in postoperative pain management has recently been implemented at TAMC as part of a multi-modal approach to treat pain. This research intended to investigate the effectiveness of the preemptive administration of rofecoxib and ibuprofen, as compared

to a placebo. Surgical patients may experience improved outcomes and shorter hospital stays due to improved postoperative pain control. This may increase patient satisfaction and decrease the cost of surgery.

Theoretical Framework

The framework for this study is based on a physiological and pharmacological model for both peripheral and central mechanisms of pain. There are principally two types of fibers that are stimulated by these mediators, A-δ and C fibers. A-δ fibers are myelinated fibers responsible for fast (first) pain, which is sharp pain. The C fibers are small, unmyelinated fibers responsible for slow (second) pain (Arnstein, 1997; Garrett, 2000). Chemicals that surround the peripheral terminals of nociceptors in the skin determine baseline sensitivity and the activation threshold (Woolf & Salter, 2000). Surgical trauma and inflammation activate the release of chemical mediators such as potassium, hydrogen, cytokines, bradykinins, histamines, serotonin (5-HT), prostaglandins, and substance P (Campbell & Halushka, 1996). These substances help to sensitize the primary afferent receptors as part of the normal physiological pain response (Cousins & Power, 1999). Multiple stimuli, as produced by surgical incision, lead to peripheral sensitization. This is due to repetitive stimulation by potent chemical mediators, which is the basis for hyperalgesia. Following injury, there is an increased sensitization to normally painless mechanical stimuli (allodynia) in a zone of "secondary hyperalgesia" in uninjured tissue surrounding the site of injury.

This sensitization is accomplished through the activation of phospholipase A_2 (PLA_2), by tissue injury, which catalyzes the conversion of arachidonic acid from

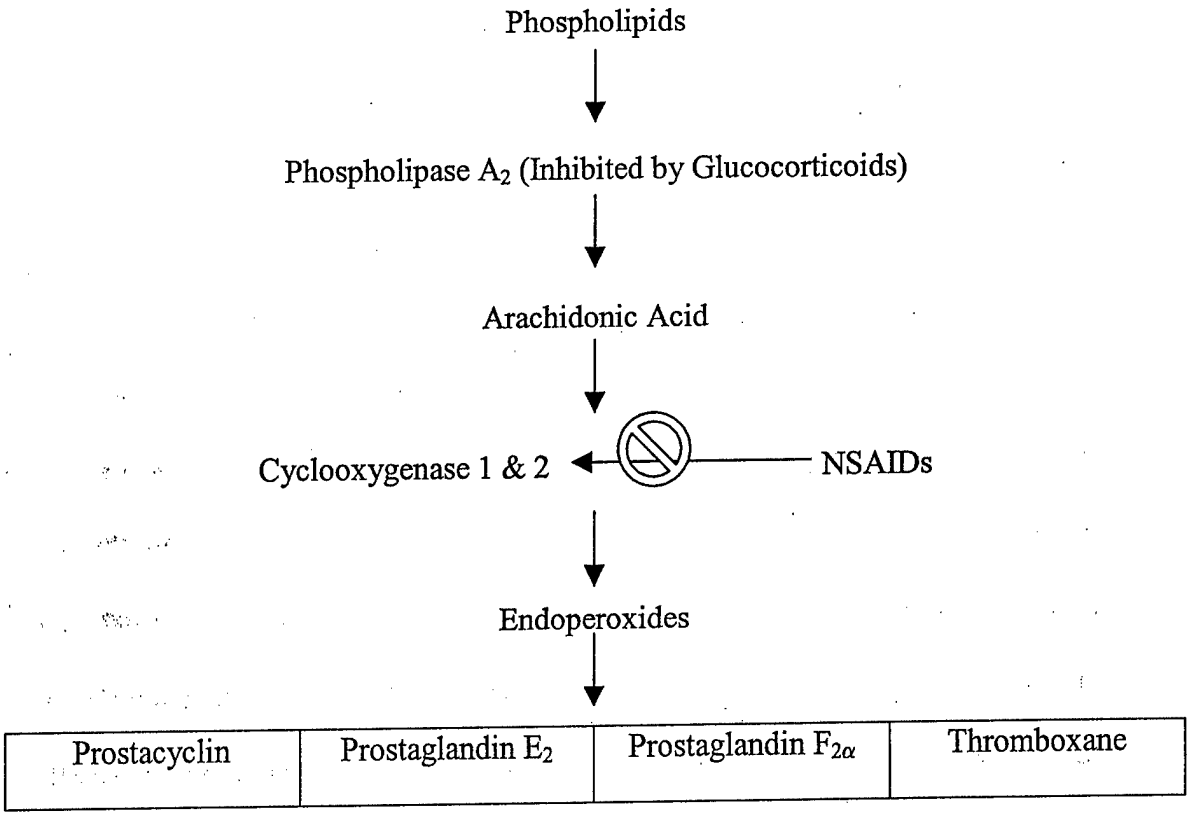


Figure 1. Physiological Framework: The Arachidonic Cascade (Insel, 1996)

phosphatidylcholine and phosphatidylethanolamine (Campbell & Halushka, 1996). Arachidonic acid is then converted to prostaglandin G_2 (PGG_2) by cyclooxygenase. This is known as the arachidonic acid pathway (Figure 1). PGG_2 is then converted to prostaglandin H_2 (PGH_2) by hydroperoxidase. PGH_2 is the precursor for many prostaglandins, prostacyclins and thromboxanes (Campbell & Halushka, 1996). Increased concentration of bradykinins, substance P, and prostaglandins leads to peripheral sensitization, which causes increased afferent input to second order neurons (Garrett, 2000). Central sensitization is the modulation of nociceptive synaptic transmission. It is triggered by peripheral nociceptor input and results in hyperalgesia and allodynia (Woolf & Mannion, 1999). Peripheral and central sensitizations are depicted on page 7 (Figure 2). The increased afferent input from peripheral sensitization causes subsequent changes in the dorsal horn neurons (Garrett, 2000). Activation of the dorsal horn neurons leads to the release of chemical mediators and activation of cyclooxygenase centrally. This may decrease the neuronal threshold for stimuli and increase the frequency of action potentials, as well as the recruitment of other neurons. This leads to continued release of glutamate, an excitatory neurotransmitter, and activation of N-methyl-D aspartate (NMDA) receptors. Activation of the NMDA receptors is important in central sensitization and in the sensation of hyperalgesia (Garrett, 2000). Central sensitization is also known as wind-up (Figure 2).

Preemptive analgesia is an attempt to attenuate acute pain by pharmacological treatment prior to surgical tissue trauma. NSAIDs given preoperatively are absorbed and distributed prior to tissue trauma. This inhibits the ensuing synthesis of prostaglandins

and the subsequent inflammatory response with the potential to reduce wind-up (Cousins & Power, 1999).

This study looked for differences in the effects of preoperative ibuprofen, a non-selective COX inhibitor, and preoperative rofecoxib, a selective COX-2 inhibitor, on postoperative pain, when compared to a placebo group. Non-selective COX inhibitors block the protective functions of COX-1 as well as those mediated by tissue trauma. Inhibition of COX-1 is responsible for the platelet dysfunction and adverse gastrointestinal and renal effects of non-selective COX inhibitors, whereas COX-2 inhibition produces anti-inflammatory effects only (Thompson et al., 2000). The use of rofecoxib is based on the premise that by blocking COX-2 alone, postoperative pain, along with adverse effects can be reduced.

Purpose

The purpose of this study was to compare the effect of the preoperative administration of oral rofecoxib 50 mg, oral ibuprofen 400 mg, or a placebo on postoperative pain relief following gynecological surgeries involving lower abdominal incisions.

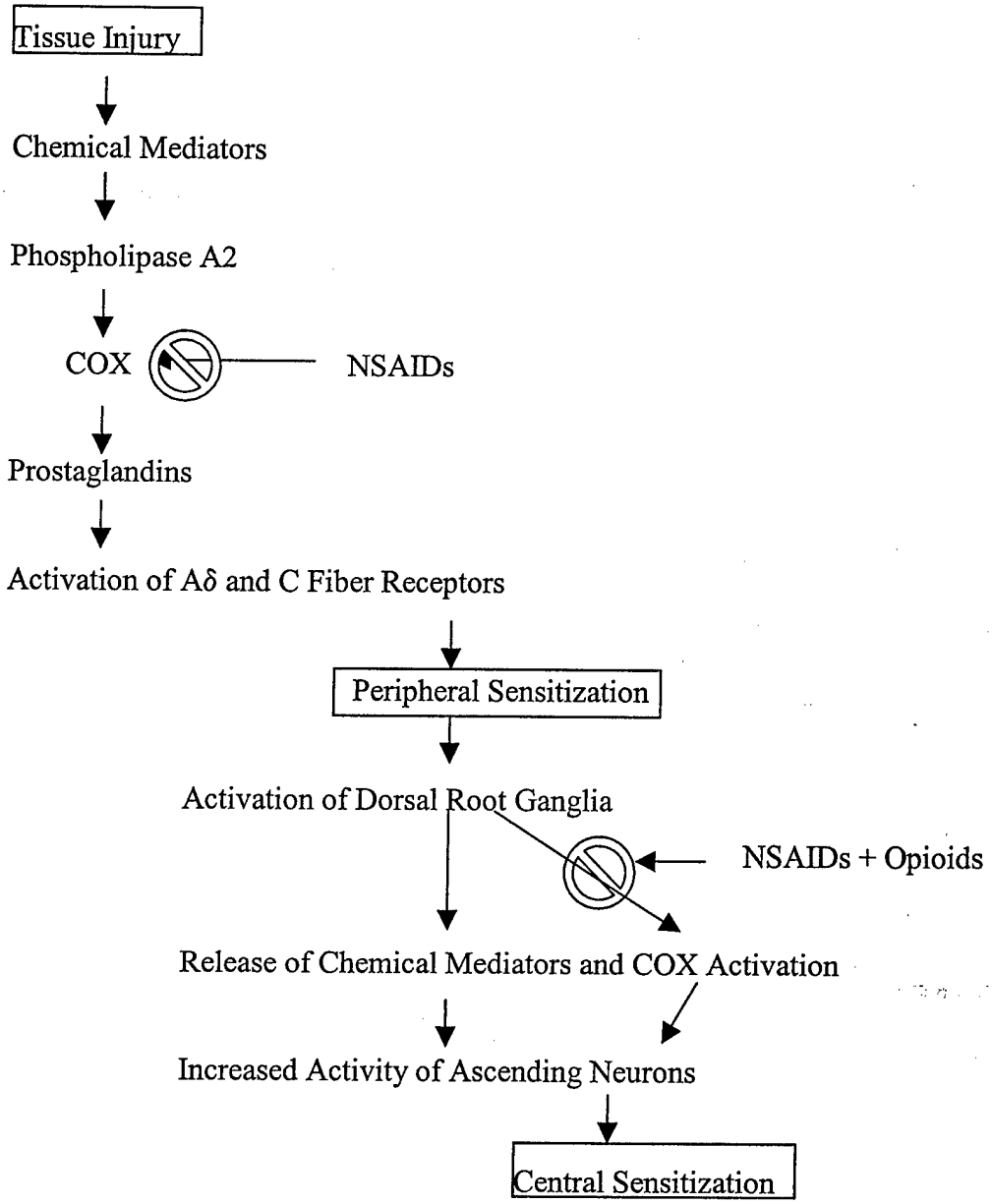


Figure 2. Physiological Framework: Peripheral and Central Sensitization (Garrett, 2000)

Definition of Terms

The following definitions were utilized for this study:

Central sensitization (wind-up).

Conceptual definition: The trauma from a surgical incision leads to peripheral sensitization (primary hyperalgesia). This stimulus leads to plasticity, causing a lower threshold, decreased response time, hyperalgesia, and allodynia (Cousins & Power, 1999).

Operational definition: Measured by the treatment groups using scores from the NRS as the patient's perception of pain and morphine consumption to evaluate the intensity of pain.

Gynecological surgery.

Conceptual definition: The surgical manipulation of female reproductive organs (Dorland, 2000).

Operational definition: All gynecological procedures involving a lower abdominal incision between January and August 2002, performed at Tripler Army Medical Center and meeting all requirements for participation in our study.

Nausea.

Conceptual definition: An unpleasant psychological sensation referred to the epigastrim and abdomen (Dorland, 2000).

Operational definition: Patient self report of nausea as noted by healthcare providers in the post anesthesia care unit (PACU) and documented on the data collection worksheet.

NSAIDs.

Conceptual definition: A group of drugs used to treat mild to moderate pain by blocking the COX enzymes (Dorland, 2000).

Operational definition: A single dose of oral ibuprofen 400 mg or rofecoxib 50 mg given one hour prior to surgical procedure.

Physical status classification (P.S.).

Conceptual definition: This system was created in 1940 to identify patients for statistical studies and hospital records. It has been used to compare surgical outcomes between different patient classifications. The purpose was to generate a means of patient comparison based on risk assessment (Role & Galloway, 2000).

Operational definition: The number assigned to the patient at their preoperative interview to designate health risk associated with surgery. A score of 1 indicates that a patient has no health risk for surgery. A score of 2 indicates that a patient has one or more associated risks that are well controlled. A score of 3 indicates that a patient has one or more associated risks that are poorly controlled. A score of 4 indicates that a patient has significant associated risks that are a constant threat to life. A score of 5 indicates a patient that is not expected to live beyond 24 hours regardless of whether they have an operation. A score of 6 indicates a patient who is designated as an organ donor. Finally, a classification of "E" indicates a patient who is requiring an emergency procedure.

Postoperative pain.

Conceptual definition: An unpleasant sensory and emotional experience associated

with actual or potential tissue damage (Bonica, 1979).

Operational definition: The severity of pain experienced by the patient following gynecological surgery involving a lower abdominal incision and was measured via the numerical rating scale (NRS) (Downie, Leatham, Rhind & Wright, 1978), at 15 time intervals. The NRS is an eleven-point pain rating scale with 0 being pain free and 10 being the worst pain imaginable.

Patient controlled analgesia (PCA).

Conceptual definition: Patient controlled analgesia is a way of giving a patient control of pain medication administration postoperatively. The patient may receive a basal rate of pain medication. In addition, they have a button to control. When pushed, this button delivers a set amount of morphine to the patient. The lockout interval is set to protect the patient from receiving a toxic dose of pain medication.

Operational definition: Study subjects were instructed on the use of PCAs preoperatively. Total morphine use was measured for 48 hours after discharge from the PACU.

Preemptive Analgesia.

Conceptual definition: Reducing the development of acute or chronic pain by treating it before it occurs. Theoretically, this can be accomplished by inhibiting pain pathways.

Operational definition: The administration of oral ibuprofen or rofecoxib one hour prior to surgery. The purpose of preemptive analgesia is to decrease postoperative

pain, which will be measured by morphine consumption and the NRS.

Vomiting.

Conceptual definition. Stomach contents forcibly expelled through the mouth (Dorland, 2000).

Operational definition. Notation by the healthcare provider in the PACU that the patient had an episode of emesis.

Research Questions

Research questions used to guide this study included:

Is there a difference between preemptive administration of rofecoxib, ibuprofen, and a placebo in the attenuation of postoperative pain in females undergoing gynecological surgery involving a lower abdominal incision?

Is there a difference in the analgesic medication required postoperatively in females undergoing gynecological surgery involving a lower abdominal incision?

Assumptions

The following assumptions were identified for this study:

1. The patient population will experience pain as a result of the surgical procedure.
2. The level of pain experienced by the patient population will be severe enough to require analgesic medication administration.
3. The administration of ibuprofen or rofecoxib is effective in the reduction of postoperative pain.
4. Opioid administration will increase the risk for nausea and vomiting.

5. PACU and surgical nurses will correctly document both the postoperative pain levels and morphine consumption.
6. The nursing staff will follow all postoperative pain management protocols set by this study and Tripler Army Medical Center.
7. Patients will accurately report the time of their last dose of an NSAID, aspirin, or opioid.

Limitations

The following limitations were identified:

1. This study may not be generalizable to other surgical populations.
2. A convenience sample of surgery patients at one hospital limits the ability to generalize our results to other populations.
3. Surgeon experience in performing these procedures may cause variations in length of surgery and the extent of tissue trauma.
4. The varying degree of experience of the anesthesia providers who provided the anesthesia may result in variations in intraoperative management.
5. Different surgical procedures have varying incisions, lengths of surgery, lengths of stay, and pain intensity.

Summary

Postoperative pain can initiate the stress response leading to increased heart rate, blood pressure, nausea, vomiting, and anxiety. This initiates a cascade of untoward postoperative outcomes such as decreased patient satisfaction, unanticipated hospital admissions, and increased overall costs. Therefore, efforts to alleviate this pain are of the

utmost importance. This randomized, double-blinded, placebo-controlled, clinical trial evaluated whether preemptive administration of rofecoxib was more effective than preemptive administration of ibuprofen, as compared to a placebo. If the preemptive administration of rofecoxib or ibuprofen is shown to be significant in reducing postoperative pain, patients may have decreased morbidity and mortality leading to better overall outcomes.

CHAPTER II

Review of the Literature

A review of current literature indicates that NSAIDs play a significant part in the treatment of postoperative pain. Recently, a new class of NSAIDs that selectively inhibit the COX-2 enzyme has been developed. COX-2 inhibitors provide therapeutic benefits with less adverse side effects than traditional NSAIDs. COX-2 inhibitors are as effective as ibuprofen in alleviating pain and they have a better side effect profile. Short-term studies demonstrate lower occurrence of gastrointestinal ulcers in patients treated with COX-2 inhibitors compared with traditional NSAIDs. In this chapter we will discuss the physiology of pain and cyclooxygenase. We will also discuss the mechanisms of action, uses, and side effects of COX-1 and COX-2 inhibitors.

Postoperative Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Nociception is the term used to describe how pain becomes conscious. The four basic principles involved in nociception are transduction, transmission, perception, and modulation. Transduction, the first principle, is the conversion of a noxious stimulus (mechanical energy) into an action potential (electrical energy). Transduction occurs in the periphery when a noxious stimulus leads to actual or potential tissue damage. The damaged cells release sensitizing substances, which lead to the generation of an action potential. The next principle, transmission, is when the action potential is conducted from the site of the noxious stimulus to the spinal cord and ascends to higher brain centers. Transmission occurs in three phases: (a) from the damaged site to

the spinal cord, (b) from the spinal cord to the brain stem and thalamus, and (c) from the thalamus the message is relayed to the cortex. The third principle, perception, is the conscious experience of pain at the level of the cortex. Modulation, the final principle, is where nociceptive impulses are also inhibited. Modulation is also referred to as the descending pain pathway. Neurons originating in the brain stem descend to the spinal cord and release endogenous substances. These endogenous substances inhibit the transmission of nociceptive impulses (McCaffery & Pasero, 1999).

The concept of wind-up must also be discussed when defining pain. Wind-up is caused by the core release of neurokinins and glutamate and can be blocked by substance P inhibitors and by glutamate antagonists. Wind-up is also blocked by anti-inflammatory drugs such as corticosteroids and cyclooxygenase inhibitors (McHugh & McHugh, 2000).

Postoperative pain is often treated with opioids. Opioids are very effective against moderate to severe pain, but they are also associated with many unwanted side effects. If the level of postoperative pain could be decreased, the need for opioids may also decrease. Preemptive analgesia is a mechanism that could possibly decrease postoperative pain. The theory associated with this phenomenon is that by providing analgesic intervention prior to surgery, one may prevent or reduce postoperative pain.

A randomized, double-blinded study done in Japan (Aida et al., 1999) evaluated the preemptive effects of epidural morphine on the following six types of surgery: (a) upper or lower limb surgery for removal of tumor or foreign body, (b) radical mastectomy, (c) gastrectomy, (d) hysterectomy, (e) herniorrhaphy, and (f) appendectomy. Preemptive analgesia was found to be effective in limb surgery and

mastectomy, but ineffective for gastrectomy, hysterectomy, herniorrhaphy, and appendectomy. The four types of surgery in which preemptive analgesia was ineffective involved visceral or peritoneal incisions. The researchers hypothesized that the reason preemptive analgesia was effective in limb and breast surgery is that the limbs and breasts are innervated only segmentally, while the abdomen and peritoneum are multiply innervated by both segmental and heterosegmental nerves. Therefore, all nociceptive stimuli from the limbs and breast areas can be entirely blocked by epidural morphine. This study concluded that preemptive epidural analgesia was effective in certain types of surgery while ineffective in others. One limitation of this study was the administration of naloxone to attenuate the prolonged effects of the intraoperative epidural morphine. The researcher's assumption was that by attenuation of the prolonged affects of intraoperative epidural morphine, further data collection would lead to comparison of preemptive data only. This reasoning, however, did not take into account the prolonged duration of epidural morphine (6-24 hours) compared to the duration of intravenous naloxone (1-4 hours) (Frandsen, 1997). Once the effects of the intravenous naloxone were attenuated due to the shorter duration, the group that received the intraoperative epidural morphine would continue to receive some postoperative pain relief.

In another study (Pasqualucci et al., 1996), researchers evaluated the effectiveness of preemptive topical bupivacaine on 120 patients undergoing laparoscopic cholecystectomy. Patients were randomly assigned to four groups; (a) Group A received 20 ml of 0.9% saline before and after surgery, (b) Group B received 20 ml 0.9% saline before surgery and 20 ml of 0.5% bupivicaine with epinephrine 1:200,000 after surgery,

(c) Group C received 20 ml of 0.5% bupivicaine with 1:200,000 epinephrine before and after surgery, and (d) Group D received 20 ml of 0.5% bupivacaine with epinephrine 1:200,000 before surgery and 20 ml 0.9% saline after surgery. The study medication was placed on the patient's peritoneum immediately after creating a pneumoperitoneum, ten minutes prior to the beginning of surgery, and at the end of the operation before the trocars were withdrawn. The results of this randomized, doubled-blinded, placebo-controlled study showed less postoperative pain intensity and analgesic consumption among patients treated preemptively. This study failed to include validity and reliability of their pain measurement instruments, the visual analog and the verbal rating pain scales. This study looked at local anesthetic application, timing, and the effect of prolonging the action of the local anesthetic. However, the researchers were unable to determine the effect of prolonging the action of the local anesthetic. The description of how this was measured was not clear.

Pitcher (2001) performed a prospective, randomized, double-blinded, placebo-controlled, pilot study on subjects undergoing laparoscopic bilateral tubal ligation. This study compared the effects over time of dextromethorphan or placebo, when given preemptively. Postoperative pain scores were measured using an 11-point numerical rating scale at eight time intervals. The data was analyzed using a one-way ANOVA. Patients who received dextromethorphan 60 mg orally before surgery had a decrease in postoperative pain ($p < 0.04$). Additionally, the amount of Roxicet ® required postoperatively was statistically less in the dextromethorphan group ($p < 0.02$) then the placebo group (Pitcher, 2001).

The results of these studies indicate that preemptive analgesia may be able to reduce postoperative pain in some populations. Additional research needs to be performed in this area.

Measurement Instruments

It was only recently that attempts to measure the severity of pain have been satisfactory. The measurement of pain in disease should not be confused with measuring experimental pain. It is easier to measure experimental pain because the exact source of the stimuli can be recorded. In pathological pain the nature of the stimulus is often unknown making measurement very difficult (Huskisson, 1974). Many of the common pain rating scales utilized to measure pain will be analyzed below.

Rating scales can be used to measure physiologic variables, such as pain, nausea, or functional capacity, using scaling techniques. Scaling is based on mathematical theory and a branch of science, which develops measurement scales (Burns & Grove, 1993).

Pain rating scales commonly used in daily clinical practice to assess pain intensity are: (a) Visual Analog Scale (VAS), (b) McGill Pain Questionnaire (MPQ), and (c) NRS. The VAS is a scale frequently used by anesthesia providers. It consists of a straight line, typically ten centimeters long, with "no pain" at one end and "pain as bad as it could possibly be" at the other. The patient makes a single mark on the line indicating his or her present level of pain (Flaherty, 1996). The clinician then measures the patient's response with a ruler. Advantages of this measurement tool include the fact that the data collected is interval data, it is simple and easy to use, and it avoids language barriers. Some disadvantages associated with the VAS are measurement error and the fact that it

cannot be administered over the phone. These measurement errors are enhanced because some patients have difficulty converting subjective pain data onto a straight line. Researchers must not photocopy the scale for research use because the 10 cm line may change slightly thus affecting the reliability of the VAS. Patients are usually sedated immediately after surgery and may not be able to accurately assign a pain score.

The MPQ uses over 75 descriptors in an effort to measure several dimensions of pain, such as: location and intensity of pain, pattern of pain over time, sensory, affective, and miscellaneous components of pain (Flaherty, 1996). The advantage to using the MPQ is that it is a powerful tool with supporting studies of its reliability and validity for obtaining quantitative and qualitative data (Flaherty, 1996). A significant disadvantage of the MPQ is that it is complex and takes up to thirty minutes to complete (Flaherty, 1996).

The NRS is an 11-point numerical rating scale. The anchors of the scale are 0 and 10, with 0 being "no pain" and 10 being the "worst imaginable pain" (Downie et al., 1978). With the NRS, the patient is asked to rate his/her pain on a scale from 0 to 10. Advantages of the NRS include the fact that it is simple to administer, easy to score, and readily administered in either written or verbal form. Although this data is considered to be ordinal in nature, many studies have shown that when utilized as interval data, the validity and reliability is equal to other measurement instruments. A study by Jensen, Karoly, and Braver (1986) compared the NRS and the VAS to determine the reliability and validity of each scale. The subjective pain measurements were analyzed using interval level data. The assumption that this data may be treated as interval level leads to

the danger of introducing distortions into the data and may throw doubt onto the conclusions of the test. However, the results of their study showed that all methods of measurement were fairly similar in terms of validity in accurately measuring pain. The NRS did rate superior to the others when considering factors such as ease of administration.

The ability to monitor patient progress and the need for analgesics is based on the ability to quantify pain intensity. The VAS is frequently used in nursing research because it generates continuous data that can be analyzed using parametric statistics. Paice & Cohen (1997) compared the VAS and the NRS in a study of 50 adult cancer patients at a large tertiary medical center. The patient's ages ranged from 19 to 76 years and they had a variety of malignancies. The correlation between the VAS and the NRS was strong and statistically significant ($r = .847$, $p < 0.001$), supporting the validity and reliability of using the NRS as interval level data.

The NRS subjectively measures the patient's pain level as stated above. Sennott-Miller, Murdaugh, and Hinshaw (1988) used magnitude-estimation scaling to measure responses recorded on a Likert scale. Magnitude estimation has several important features that are instrumental in the measurement of subjective nursing research data: interval-ratio scales are generated and the judgments given are repeatable and stable with test-retest reliability coefficients near (r) = .90. Magnitude estimation has been shown to be reliable and valid in using subjective data as interval data. Since the NRS scale produces estimates of validity and reliability similar to the VAS and has been successfully utilized in previous clinical trials at TAMC it was utilized in this study. The

patient's subjective pain level can be recorded as interval level data.

Cyclooxygenase

Definitions

Fatty acid cyclooxygenase, also called prostaglandin endoperoxide synthase, is an enzyme that catalyzes the conversion of arachidonic acid to various types of prostaglandins and thromboxanes (Lehninger, Nelson, & Cox, 1993). To understand cyclooxygenase, first a basic understanding of arachidonic acid and eicosanoids is required.

Arachidonic acid is a 20-carbon polyunsaturated fatty acid. It is produced from membrane phospholipids via phospholipase-A_2 in response to a hormonal or other stimulus, such as surgical trauma. All eicosanoids are derived from arachidonic acid. There are four classes of eicosanoids: thromboxanes, prostaglandins, prostacyclins, and leukotrienes. These molecules act as short-range messengers affecting tissues near the cells that produce them. Cyclooxygenase inhibitors, to include NSAIDs and aspirin, interrupt the arachidonic acid pathway.

The production of the leukotrienes is a separate pathway involving arachidonic acid and lipooxygenases. NSAIDs and aspirin do not affect this pathway (Lehninger et al., 1993).

There are two catalytic activities in the synthesis of prostaglandins. The first is the conversion of arachidonic acid to PGG2 with cyclooxygenase as the catalytic enzyme. The second is the conversion of PGG2 to PGH2 with hydroperoxidase as the catalytic enzyme. PGH2 is the immediate precursor to many other prostaglandins and

thromboxanes (Lehninger et al., 1993). Prostaglandins are formed centrally and peripherally (Figure 1).

Types and Functions

There are two isoforms of cyclooxygenase, COX-1 and COX-2. COX-1 is constitutively expressed in most tissues. COX-1 is responsible for mediating basic physiologic functions, including gastrointestinal mucosal function and vascular hemostasis. Interruption of these functions leads to many of the common side effects of NSAIDs. COX-2 is not normally expressed, but is induced by various factors including cytokines and growth factors, leading to the production of prostaglandins. The prostaglandin synthesis has two functions. The first is the formation of cyclic endoperoxide prostaglandin G through the enzyme cyclooxygenase. The second is the conversion of PGG to prostaglandin H by a peroxidase activity (Campbell & Halushka, 1996).

Eicosanoids are responsible for a variety of different functions. Prostaglandin E2 (PGE2) and prostacyclin cause erythema and increase local blood flow mediating the inflammatory response (Campbell & Halushka, 1996). Many other substances including bradykinin, leukotrienes, serotonin (5-HT), and platelet activating factor are also important in mediating the inflammatory response. The inflammatory response leads to increased pain in the inflamed tissue, this is known as hyperalgesia. Prostaglandins cause pain that has a slower onset but lasts longer than pain caused by bradykinin or histamine. Leukotrienes are also associated with hyperalgesia. Leukotrienes and prostaglandins are released by the inflammatory process and work to amplify the pain mechanism through

modulation (Campbell & Halushka, 1996). The fact that COX-2 is inducible suggests that it plays a major role in inflammation and cell growth.

Eicosanoids exhibit many other effects depending on the type of tissue. In the cardiovascular system most prostaglandins are potent vasodilators of arterioles, precapillary sphincters, and postcapillary venules. In the mesenteric, coronary, and renal vascular beds the prostaglandin D_2 (PGD_2) causes more vasoconstriction than vasodilation. PGD_2 causes only vasoconstriction in the pulmonary circulation. Prostaglandins also have a weak, direct inotropic effect that cause increased cardiac output. Leukotrienes cause hypotension, which is thought to be due to a decrease in intravascular volume and cardiac contractility (Campbell & Halushka, 1996).

Eicosanoids modify the function of formed elements in the blood, in particular, platelets. Thromboxane A_2 is an important arachidonate metabolite in platelets, causing platelet aggregation and vasoconstriction. Li, Su, & Chapleau (1995) found in a study on 22 New Zealand white rabbits, that the normal endothelium may serve a protective role in inhibiting platelet aggregation and in opposing platelet-induced suppression of baroreceptor activity. This is mediated through the release of prostaglandin I_2. Aspirin binds covalently to the cyclooxygenase enzymes in platelets impairing platelet aggregation for the life of the platelet, 8-11 days (Li et al., 1995).

Eicosanoids are responsible for contraction or relaxation in smooth muscles. They are important in normal gastrointestinal function, kidney function, and urine formation. Eicosanoids also stimulate or depress the central nervous system. Prostaglandins increase the circulating concentrations of adrenocorticotropic hormone,

growth hormone, prolactin, and gonadotropins, as well as stimulate steroid production, insulin release, and progesterone secretion (Campbell & Halushka, 1996).

NSAIDs as Non-selective Cyclooxygenase Inhibitors

Types

The NSAIDs are a heterogeneous group of medications that possess varying degrees of anti-inflammatory, analgesic, and antipyretic properties. They also share common side effects. Aspirin is the prototype; this group is commonly referred to as aspirin-like drugs (Insel, 1996).

NSAIDS are organic acids and are classified based on their chemical structures. There are several groups of NSAIDs, each containing unique chemical structures. The groups include salicylic acid derivatives, para-aminophenol derivatives, indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids and alkanones (Insel, 1996). Ibuprofen was the first drug in the arylpropionic class.

Dionne, Campbell, Cooper, Hall, & Buckingham (1983), in a randomized and double-blinded study, evaluated the analgesic effect of preoperatively administrated ibuprofen to 107 outpatient subjects undergoing the removal of impacted third molars. They were given ibuprofen 800 mg preoperatively and ibuprofen 400 mg four and eight hours postoperatively. Comparison groups were given either a placebo on the same schedule, acetaminophen 600 mg on the same schedule, or placebo preoperatively followed by two postoperative doses of 600 mg acetaminophen plus codeine 60 mg on the same schedule. Pain intensity was recorded hourly for twelve hours, on a category rating scale in which the subjects rated their pain as none (0), slight (1), moderate (2), or

severe (3). The hourly pain intensity scores were summed at the 2, 3, and 4-hour observations.

The pain scores revealed that the ibuprofen group reported significantly less pain than the placebo or acetaminophen group ($p < 0.001$). The sum of the pain intensity scores taken after the second dose given at the four hour marker revealed that ibuprofen resulted in significantly less pain than placebo ($p < 0.001$), acetaminophen ($p < 0.01$), and acetaminophen plus codeine ($p < 0.02$). This study supports the idea that ibuprofen can result in decreased postoperative pain scores when given preoperatively. No information was provided on the reliability and validity of the pain assessment tool. The rank order data was treated as interval data in their study.

In a 1995 study, Dahl, Raeder, Drosdal, Wathne, & Brynildsrud compared ibuprofen, ibuprofen plus codeine, and placebo in subjects undergoing hip arthroplasty. In this experimental study, all subjects were given regional anesthesia for the surgery. Before recovery from spinal anesthesia, the 123 randomly assigned subjects were given ibuprofen 800 mg, ibuprofen 800 mg plus codeine 60 mg, or a placebo. The researchers observed the subjects for five hours postoperatively. Pain was measured using a standard 0-100mm VAS and a verbal pain scale where pain was reported as none (0), slight (1), medium (2), strong (3), or extremely strong (4). The amount of analgesia (ketobemidone) required postoperatively was recorded for each subject. Ketobemidone is a highly addictive narcotic ketone related chemically to meperidine (Fasthealth, 2000). Bleeding was assessed using a dressing with vacuum drainage applied. Incidence of nausea was also recorded for each subject.

The results showed that the placebo group received 45% more ketobemidone postoperatively than the other two groups ($p < 0.001$). The placebo group reported significantly higher pain scores at two and four hours on the verbal scale ($p < 0.05$) using the Kruskal-Wallis test and significantly higher after four hours on the VAS ($p < 0.001$) using an ANOVA-variance test. There was no significant difference on evaluation of pain or opioid received between the ibuprofen group and the ibuprofen plus codeine group. There was no significant difference in bleeding or side effects between any of the three groups. This study concluded that ibuprofen could result in decreased postoperative pain scores and opioid use when given preemptively.

Law, Southard, Law, Logan, & Jakobsen (2000) performed a randomized, double-blinded study to evaluate the effectiveness of preoperative ibuprofen in decreasing the incidence of pain after orthodontic separator placement. Sixty-three adolescent patients were randomly assigned to receive either: (a) 400 mg ibuprofen taken orally one hour before surgery and a placebo immediately after the procedure, (b) placebo taken orally one hour prior to surgery and 400 mg ibuprofen taken immediately following the procedure, (c) placebo taken orally one hour prior to surgery and placebo taken immediately after the procedure. The patient's pain levels were measured with the VAS at 2, 6, and 24 hours, as well as 2, 3, and 7 days following surgery. An analysis of variance revealed that 2 hours after their orthodontic appointment, the patients who had taken ibuprofen 1 hour before the procedure had significantly ($p < 0.05$) less pain with chewing than the other two groups. These results support the use of preemptive analgesics in orthodontics.

Gibbons & Harm (2000) performed a prospective, randomized, double-blinded clinical trial, which compared the effects over time of preemptive ketorolac or ibuprofen in patients undergoing bilateral tubal ligation. The sample comprised 44 PS category I or II patients randomized to one of two treatment groups: 800 mg ibuprofen orally and 1 ml saline placebo intravenously or oral placebo and ketorolac 30 mg intravenously. Postoperative pain was assessed using an 11-point numerical rating scale at seven time intervals. Pain scores were assessed using a two-way repeated measures ANOVA with orthogonal contrasts. Analysis revealed a significant difference, with the group receiving ibuprofen having lower postoperative pain scores ($p < 0.01$) from two hours after the end of the surgery until bedtime (Gibbons & Harm, 2000). There study did not use a negative control in order to show overall effectiveness of preemptive analgesia.

Uses of NSAIDs in Acute Postoperative Pain and Gynecological Patients

This section covers the use of NSAIDs in women who have disorders or surgeries pertaining to the female reproductive tract. Ketorolac, a parenteral NSAID, has been used extensively to provide postoperative analgesia (Cataldo, Senagore, & Kilbride, 1993; Diemunsch, Diemunsch, & Treisser, 1997; Green et al., 1996; Schoneboom, 1992). Green et al. (1996) performed a study to evaluate whether ketorolac would act synergistically with fentanyl to decrease postoperative analgesic requirements and whether or not pain scores were reduced in gynecological patients. This stratified, randomized, double-blinded study evaluated the postoperative analgesic requirements and pain scores of 126 patients following tubal ligation or diagnostic laparoscopy.

The results showed that intraoperative ketorolac 60 mg intravenously (IV) with fentanyl 2 mcg/kg IV, administered at the induction of anesthesia resulted in significant ($p < 0.05$) postoperative opioid sparing and decreased perception of pain. The results were significant only with patients undergoing diagnostic laparoscopic surgery and not with patients undergoing laparoscopic tubal ligations. There was also a lower incidence of nausea and vomiting in the diagnostic laparoscopic group (Green et al., 1996). These results demonstrated that the pain after a laparoscopic tubal ligation is far greater than the pain following a diagnostic laparoscopic surgery. Researchers mention that this difference in pain between groups may help in the design of a better pain control regimen, however, they do not allude to the reasons for this difference. This suggests that these procedures should be considered separately when designing analgesic regimens (Green et al., 1996).

Ketorolac has been used to decrease postoperative opioid use. Cataldo, Senagore, & Kilbride (1993) performed a prospective, randomized study comparing intramuscular ketorolac in combination with PCA morphine (PCA-M), compared to PCA-M alone in controlling patient pain following colon resection. Ketorolac 30 mg, was administered immediately after surgery and every six hours for the next 72 hours. Thirty patients were involved in this three month long study, 17 were assigned to group 1 (ketorolac & PCA-M) and 13 to group 2 (PCA-M alone). Cataldo et al. (1993) found narcotic use to be 45% less when ketorolac and PCA-M were used simultaneously following colon resection as compared to patients only using the PCA-M. The incidence of side effects, including atelectasis, confusion, and drowsiness was equally distributed

between the two groups. However, elderly and chronic obstructive pulmonary disease patients who are prone to narcotic related complications may benefit from the combination of ketorolac and the PCA-M because of the reduced opioid use associated with this method.

Benefits of NSAIDs

NSAIDs have varying degrees of analgesic, antipyretic, and anti-inflammatory actions. As analgesics, the NSAIDs are effective in the treatment of low to moderate pain. They have a much lower maximal effect and lack the unwanted side effects of opioids, such as central nervous system and respiratory depression, constipation, and the development of physical dependence. They are particularly effective against postoperative pain and pain arising from inflammation (Insel, 1996).

NSAIDs decrease the cost of additional medical care that would be incurred to treat the untoward side effects of opioid analgesics. Ibuprofen is often used as an adjunct to opioids for postoperative pain management. This combination can decrease pain for the patient. This improves patient outcomes and satisfaction. (Dahl et al., 1995; Owen, Galvin, & Shaw, 1986).

Owen, Glavin, and Shaw (1986) performed an quasi-experimental study to evaluate the effect of ibuprofen on pain, morphine requirements, nausea, and blood loss following abdominal surgery. Seventy-one subjects were randomly assigned to receive either an ibuprofen 500 mg suppository 60-90 minutes prior to surgery and then every eight hours for 24 hours, or a placebo on the same schedule. Pain was rated on a nine-point descriptive rating scale ranging from no pain to very severe pain. Nausea was recorded at

six hours and 24 hours on a four-point scale. Neither scale was well described in the report. Bleeding was recorded by swab weighing. Morphine consumption was tracked by the PCA. There were no significant differences between the groups for pain, bleeding, or nausea. The consumption of morphine was significantly higher ($p < 0.05$) for the group receiving the placebo compared to the group receiving ibuprofen (Owen et al., 1986). This study, and the previously mentioned study by Dahl et al. (1995), supports the idea that preemptive administration of ibuprofen can decrease opioid use.

Dalton et al., (2000) analyzed the costs of postoperative pain medications before and after an educational program regarding pain. This program was administered to nurses, pharmacists, and physicians in six community hospitals. They looked at the cost of pain medication for different operations and the relationship of the cost of medication to the length of stay, function, and pain intensity. The researchers found that patients undergoing major lower abdominal procedures had the highest mean NSAID cost ($43.98), highest mean opioid cost ($7.78), and highest mean agonist-antagonist medication cost ($18.44). The cost of combination therapy for all surgeries studied ranged from $0.97 to $2.97. The cost of treating side effects of opioid administration was also evaluated. The study found that 361 of the 660 patients who received opioids also were treated with antiemetics for a total cost of $1195.85 (mean $3.31). This is compared to the 39 out of 119 patients who did not receive opioids but were treated for nausea. The cost of their treatment was $91.28 (mean $2.34). There was a 42% increase in the mean cost of treating nausea in patients who received opioids as compared to those who did not. However, the mean cost of combination opioids was less than the mean cost

for opioids as compared to length of stay. This study did not look at the effect of medications given preoperatively to attenuate pain and the relationship to cost and length of stay.

Side Effects and Contraindications

The NSAIDs share several untoward side effects. The most common side effect is gastric irritation and ulceration. Previous studies support the correlation of gastroduodenal side effects and NSAIDs due to the inhibition of COX-1 (Bjarnason, Macpherson, Rotman, Schupp, & Hayllar, 1997; Hirata, Ukawa, Kitamura, & Takeuchi, 1997). COX-2 inhibitors spare COX-1 inhibition.

Hirata et al. (1997) performed an experimental study using male Sprague-Dawley rats to compare the effects of the COX-2 inhibitor nimesulide and NS-398 to the non-selective COX inhibitor indomethacin on duodenal bicarbonate (HCO_3^-) secretion and ulcerogenic responses to mucosal acidification. Four groups consisting of four to six rats were pretreated with saline, indomethacin (10 mg/kg), NS-398 (10 mg/kg), or nimesulide (10 mg/kg), respectively. Duodenal HCO_3^- secretion was measured by the pH-stat system, which was not well defined in this report. The rats were pretreated 60 minutes prior to the experiment with the medications previously mentioned. The duodenal loop was then rinsed with saline and the HCO_3^- secretion was measured. To stimulate HCO_3^- secretion, the loop was perfused for 10 minutes with 10mM of hydrochloric acid (HCl) that was made isotonic with sodium chloride (NaCl). The loop was rinsed again with saline after acid perfusion and the HCO_3^- secretion was measured again.

The results indicated that the group receiving indomethacin showed a significant decrease in secretion upon acidification ($p < 0.05$). The groups receiving saline, NS-398, and nimesulide had no effect on basal secretion or the increase in secretion upon acidification. The rats in each group were given IV histamine (8 mg/kg/hr) for six hours. The duodenum was removed and a blinded researcher analyzed the ulcerations with a dissecting microscope. The criteria for ulceration was not well defined in this report. However, the ulcerogenic lesions in the group that received indomethacin were significantly higher in number than the other three groups ($p < 0.05$). The groups receiving NS-398 and nimesulide did not significantly differ from the saline control group (Hirata, 1997). This study did not include descriptions of the scales used or reliability and validity information on the scales.

Bjarnason et al. (1997) performed an experimental crossover study to compare the gastrointestinal side effects between a COX-2 inhibitor (flusolide) and the non-selective COX inhibitor naproxen in 19 subjects with osteoarthritis. The subjects were randomly assigned to two groups. Endoscopy was performed to evaluate and assure that no ulcerations were detected. One group then received flusolide 20mg twice a day for two weeks. Two to four hours after the last dose the endoscopy was repeated. They then underwent a two-week washout period and at the end underwent endoscopy. The patients then received naproxen 500 mg twice a day after a normal endoscopy. Two to four hours after the last dose of naproxen the endoscopy was repeated to assess for gastrointestinal ulcerations. The second group underwent the same therapy except, in the first phase, they were given naproxen 500 mg twice a day, and following the washout period were

given flusolide 20 mg twice a day. The primary scale used to measure gastroduodenal ulceration was the Lanza scale. Damage was scored as "no damage" (0), one submucosal hemorrhage or superficial erosion (1), 2-5 submucosal hemorrhages or superficial erosions (2), 5-10 submucosal hemorrhages or superficial erosions (3), and more than 10 submucosal hemorrhages or superficial erosions (4). No additional information or reliability and validity were included for this scale.

Results showed that flusolide was associated with significantly less gastric damage (although this is ordinal data the study reported a mean Lanza score = 0.58) than naproxen (mean Lanza score = 1.47) with $p = 0.0006$. The Gastroscopic Rating Scale (GRS) was used as a secondary evaluation measure. The gastric and duodenal appearances were scored as no damage (0), hyperemia and/or 1-3 erythematous areas (1), more than 3 erythematous areas (2), 1-3 submucosal hemorrhages (3), more than 3 localized submucosal hemorrhages (4), widespread submucosal hemorrhage (5), 1-3 erosions (6), more than 3 erosions (7), a single ulcer (8), and multiple ulcers (9). The GRS also showed flusolide was associated with less gastric damage. This study also treated the ordinal data as interval data and reported a mean GRS score = 1.47. Naproxen resulted in a mean GRS score = 3.84 with $p < 0.005$. There was no significant difference in duodenal damage between these two medications. The results of these studies endorse the idea that COX-2 inhibitors are associated with less gastrointestinal side effects when compared to conventional NSAIDs, probably due to the sparing of the cytoprotective COX-1. This study treated the ordinal data of these two scales as interval data; no information was available on the reliability and validity of these scales as well as any

discussion of their use as interval data. Identified weaknesses of this study stem from the assessment of gastric damage due to intra- and inter-observer variability.

A second side effect of NSAIDs is inhibition of platelet aggregation by preventing the synthesis of thromboxane A2, a potent aggregating agent. This inhibition can result in an increase in bleeding time. Aspirin is the most effective inhibitor of platelet aggregation due to its irreversible action on cyclooxygenase. NSAIDs have also been shown to prolong gestation by blocking the synthesis of prostaglandins in the E and F series, which are uterotropic (Insel, 1996).

Diemunsch et al. (1997) performed a case study on a 39 year old primipara, who was undergoing a cesarean section, that developed uterine atonia following ketorolac 30 mg given intravenously. The patient's medical history included an allergy to beta-lactams and pyuritic urticarial papules. The cesarean section was performed under lumbar epidural anesthesia using bupivicaine. The patient's blood loss was 400 cc and the urine output was 100 cc. The postoperative analgesia consisted of a paracetamol pro-drug, propacetamol 2 g in 5% dextrose and ketorolac 30 mg intravenously. Paracetamol is a parenteral form of acetaminophen. Ketorolac inhibits platelet aggregation and thromboxane production, prolonging bleeding time by 135%. Diemunsch et al. (1997) found it important to avoid NSAIDs as postoperative analgesia where risk factors for bleeding are present. Sudden hemorrhage and uterine atonia occurred 2 hours after the infusions. This case study emphasizes the importance of excluding the use of NSAIDs in patients at increased risk for bleeding.

NSAIDs inhibit prostaglandin-mediated renal function. They have little effect on normal patients due to the limited role of vasodilatory prostaglandins in the normal functioning kidney. However, NSAIDs can play a major role in renal blood flow and glomerular filtration rate in conditions such as congestive heart failure, chronic renal disease, or hypovolemia during surgery (Clive & Stoff, 1984). Clive & Stoff, (1984) hypothesized that volume contraction due to sodium depletion activates the adrenergic and renin-angiotensin responses, causing constriction of the renal vessels. The vasodilatory effects of renal prostaglandins attenuate these responses. NSAIDs inhibit the actions of the renal prostaglandins contributing to impaired renal hemodynamics.

The most serious contraindication to the NSAIDs is a hypersensitivity to the medication. There is up to a 25% occurrence of hypersensitivity in middle-aged patients with a history of asthma, nasal polyps, or chronic urticaria. This can manifest anywhere from generalized urticaria to bronchoconstriction, hypotension, and shock (Insel, 1996). Although this reaction can resemble anaphylaxis, it appears to be non-immunologic in nature. A person who is intolerant to a particular NSAID may react with any of the other NSAIDs, despite their chemical diversity. Other contraindications include active gastrointestinal bleeding or a history of NSAID induced asthma (Insel, 1996).

An article by Bonnel, Maria, Karwoski, & Beitz. (2002) addressed the occurrence of aseptic meningitis associated with the use of rofecoxib. There have been seven U.S. cases of aseptic meningitis reported to the Food and Drug Administration from May 1999 to February 2001. All patients became symptomatic after one to twelve days of rofecoxib

therapy. The authors suggest, that as with other NSAIDs, rofecoxib should be considered in the differential diagnosis of aseptic meningitis.

Selective Cyclooxygenase-2 Inhibitors

Types

COX-1 and COX-2 act as rate-limiting enzymes in prostaglandin and thromboxane synthesis. COX-1 is expressed at fairly constant levels in cells, including the gastrointestinal mucosa and platelets. Expression of COX-2 is regulated. In many cells, levels of COX-2 can be increased dramatically by various stimuli, including inflammatory cytokines, bacterial toxins, and growth factors. It is thought that COX-2 plays an important role during the inflammatory process, infection, and cellular proliferation (Feldman & McMahon, 2000). Induction of cyclooxygenase leads to an increase in adhesion molecule expression, activation of B-cells, T-cells, natural killer cells, and production of other cytokines (Insel, 1996).

There is increasing interest concerning the side effects and efficacy between traditional non-selective cyclooxygenase inhibitors and selective COX-2 inhibitors. Newly developed drugs designed to selectively block COX-2 are thought to have anti-inflammatory properties without causing gastrointestinal side effects and platelet dysfunction. Two selective COX-2 inhibitors used in the U.S. are celecoxib and rofecoxib. Celecoxib and rofecoxib are available for use in patients with osteoarthritis. Celecoxib is approved for the treatment of rheumatoid arthritis, while rofecoxib is approved for the treatment of acute pain and menstrual pain (Feldman & McMahon, 2000). Selective COX-2 inhibitors and non-selective COX inhibitors result in similar

decreases of cytokine-mediated responses at sites of inflammation. Morbidity and mortality associated with use of traditional NSAIDs could be decreased by use of COX-2 inhibitors due to maintenance of physiological COX-1 expression. In addition, prophylaxis for ulcers could become unnecessary in patients receiving COX-2 inhibitors (Feldman & McMahon, 2000).

A study conducted at the Mayo Clinic (Bensen et al., 1999) compared the efficacy and safety of celecoxib with the non-selective COX inhibitor naproxen in the treatment of osteoarthritis of the knee. In this multicentered, randomized, double-blinded, placebo-controlled clinical trial, 1003 male/female patients aged 18 years and older with symptomatic osteoarthritis of the knee were randomly assigned to receive celecoxib at doses of 50 mg, 100 mg, or 200 mg twice a day, naproxen 500 mg twice a day, or placebo twice a day, for 12 weeks. Patients were assessed for arthritis pain with standard measures of efficacy using a visual analog scale (VAS), Patient's and Physician's Global Assessment of Arthritis Scale (PGAAS), Osteoarthritis Severity Index (OSI), and the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. Assessments were performed 2 to 7 days after stopping previous NSAID or analgesic therapy and after 2, 6, and 12 weeks of treatment with the study medication.

Celecoxib treatment led to significant improvement ($p < .05$) in the signs and symptoms of osteoarthritis determined by all measurement scales implemented during the study. In the celecoxib and naproxen groups pain relief was greater than the placebo group. This was significant ($p < 0.05$) within two days of beginning treatment. Maximum anti-inflammatory and analgesic activity, evident within two weeks, was

sustained throughout the twelve-week study for all groups except the placebo group. Dosing regimens of celecoxib (100 and 200 mg twice a day) had comparable efficacy to naproxen (500 mg twice a day). Both celecoxib and naproxen were well tolerated. Researchers concluded that COX-2 inhibition with celecoxib is an effective approach for the treatment of osteoarthritis. The strengths of this study include a large study population, the use of assessment tools with well-established validity and reliability, and conventional methods of measuring osteoarthritic pain. The major criticism of this study is that the PGAAS is subjective to the physician performing the score. The subjectivity of the physician performing the score may enter bias into the study.

In a similar study, Day et al. (2000) compared the efficacy and safety of rofecoxib with ibuprofen. In this randomized, double blinded trial, 809 adults with osteoarthritis were randomly assigned to receive rofecoxib 12.5 or 25 mg once daily, or ibuprofen 800 mg three times daily. Both doses of rofecoxib demonstrated clinical efficacy comparable with ibuprofen as assessed by pain walking on a flat surface, WOMAC, patient global assessment of response to therapy, and investigator global assessment of disease status. All treatments were well tolerated. The incidence of adverse effects was not significant between the two drugs ($p > 0.05$). Researchers concluded that rofecoxib provided clinical efficacy comparable with a high dose ibuprofen regimen.

A study by Saag et al. (2000) compared the efficacy of rofecoxib with other NSAIDs in patients with osteoarthritis. The placebo-controlled study was conducted over a 6-week trial with 736 patients, randomized and double-blinded to groups. The groups consisted of rofecoxib either 12.5 mg or 25 mg given once daily, or ibuprofen 800 mg

given 3 times daily. This study was compared to another randomized double-blinded study conducted over a year with 693 patients. The groups consisted of rofecoxib 12.5 mg or 25 mg given once daily and diclofenac 50 mg given three times daily. Acetaminophen 325 mg was given for breakthrough pain. Researchers evaluated pain walking on a flat surface using the WOMAC and the 100-mm VAS. A patient global response to therapy was assessed using a Likert like scale with 0 being none and 4 being excellent. Acetaminophen use was recorded at each visit. The study found that rofecoxib at both doses demonstrated efficacy that was clinically comparable to ibuprofen and to diclofenac. This study did not attempt to establish a difference in onset of pain relief or in duration of pain relief.

A review of the literature shows a well-established use of celecoxib, rofecoxib, and ibuprofen when comparing COX-inhibitors. In addition, these medications have been shown to be both efficacious and safe in the treatment of pain. Studies that were reviewed included randomized, double-blinded, prospective, trials, many included a placebo. These studies looked at the effects of preemptive analgesia in different surgical models. The results have been mixed and clearly showed that there remains the need for additional studies in preemptive analgesia.

COX-2 Inhibitor Mechanism of Action

COX-2 is not thought to be constitutively expressed, but rather is induced in inflammatory states (Reuben & Connelly, 2000). The COX-2 inhibitors prevent the conversion of arachidonic acid to PGG2 and subsequently to PGH2, thereby preventing the formation of thromboxane-A2 (Feldman & McMahon, 2000). PGH2 and

thromboxane-A2 are believed to mediate the pain and inflammatory responses. This is contrary to COX-1, which is constitutively expressed. Since the COX-2 selective inhibitors do not inhibit COX-1, it can continue its "housekeeping" role in protecting the gastrointestinal epithelial lining against ulceration (Feldman & McMahon, 2000) (Figure 1).

Uses of Cyclooxygenase-2 Inhibitors

The three primary COX-2 inhibitors that are approved by the Food and Drug Administration (FDA) have been approved for slightly different indications (Noble, King, & Olutade, 2000). Celecoxib 100 mg twice daily and 200 mg once daily have been approved for the treatment of rheumatoid arthritis and osteoarthritis. Meloxicam 7.5 mg per day has been approved for use in the treatment of osteoarthritis. Rofecoxib 12.5 to 25 mg once daily has been approved for the treatment of osteoarthritis, primary dysmenorrhea, and 50 mg once daily for acute pain. Celecoxib and rofecoxib can be administered without regard to meals. They are well absorbed through the gastric mucosa and reach peak concentrations in approximately three hours (Noble et al., 2000).

Malmstrom, Daniels, Kotey, Seidenberg, and DesJardins (1999) compared the efficacy of celecoxib 200 mg, rofecoxib 50 mg, and ibuprofen 400 mg in an acute postoperative dental pain model. The randomized, single-dose, double-blinded, placebo and active-comparator-controlled, parallel-group study evaluated the pain and pain relief of 272 patients after having two or more third molars removed by using the Total Pain Relief (TOPAR) scale. The TOPAR assesses total pain relief over 8 hours. The results showed that rofecoxib had superior analgesic efficacy compared to celecoxib ($p < 0.001$).

Rofecoxib had similar pain relief scores as ibuprofen but with a longer duration of pain relief. Rofecoxib's duration of pain relief was greater than twenty-four hours ($p < 0.001$), compared to 8.9 hours with ibuprofen. Rofecoxib was superior to celecoxib in overall analgesic effect, time to onset of effect, peak pain relief, and duration of effect ($p < 0.001$).

In the study conducted by Reuben and Connelly (2000), a single oral dose of either celecoxib 200 mg or rofecoxib 50 mg was administered to orthopedic patients prior to spinal fusion surgery. Both drugs demonstrated a significant opioid sparing effect postoperatively. However, rofecoxib had a significantly greater duration of analgesic effect ($p < 0.01$).

Huang, Taguchi, Hsu, Andriole, & Kurz (2001) performed a randomized, double-blinded, prospective experiment to evaluate the effectiveness of oral rofecoxib 50 mg, given preemptively, to decrease postoperative pain and morphine consumption following radical prostatectomy. Thirty PS I, II, and III patients were randomly assigned to receive either: rofecoxib 50 mg orally or a placebo one hour prior to the induction of anesthesia. Patients were instructed on the use of the PCA pump in the recovery room. Patient generated VAS scores for pain and morphine consumption were collected at 1, 2, 4, 6, 8, and 24 hours after surgery. Study results revealed that there was no significant difference in postoperative pain scores or morphine consumption between the rofecoxib or placebo group. This study evaluated pain scores and morphine consumption for only 24 hours. Our study evaluated these variables over a 48-hour timeframe. Additionally, the type of procedure determines the severity of postoperative pain. Radical prostatectomies are

associated with a high degree of postoperative pain. This high degree of pain may make NSAIDs relatively ineffective in contributing to analgesia.

Benefits of Cyclooxygenase Inhibitors

NSAIDs have been the mainstay of clinical care for musculoskeletal disorders (Silverstein et al., 2000), dental pain, postoperative pain, minor pain, and inflammation. Though generally considered safe, NSAID use has been implicated in gastrointestinal complications including ulceration and hemorrhage. It is believed that COX-2 inhibitors can provide analgesia comparable to non-selective NSAIDs, but without the gastrointestinal toxicity complications (Feldman & McMahon, 2000). Furthermore, COX-2 inhibitors are not considered to alter normal platelet function or renal blood flow (Noble et al., 2000), and may provide possible protection from colon cancer (Silverstein et al., 2000).

COX-2 inhibitors appear to be as effective as traditional NSAIDs in relieving pain and inflammation. The real benefit of COX-2 inhibitors appears to be in their more favorable side effect profile and longer duration of action (Reuben & Connelly, 2000). The COX-2 inhibitors are more expensive than NSAIDs; therefore, the decision to use them should be based on the patient's risk of gastrointestinal tract complications (Noble et al., 2000).

Metabolism

Celecoxib and rofecoxib are metabolized hepatically, celecoxib by the cytochrome P450 system, and rofecoxib by cytosolic enzymes (Noble et al., 2000). Rofecoxib is not recommended for use in patients with moderate to severe hepatic disease. Celecoxib can

be used at lower doses in patients with moderate, but not severe hepatic disease, though hepatic enzymes should always be monitored if hepatic dysfunction is suspected (Noble et al., 2000).

Side Effects and Contraindications

The side effects of COX-2 inhibitors include abdominal pain, dyspepsia, and diarrhea, as well as worsening of hypertension and edema (Noble et al., 2000). Therefore, they should be used cautiously, if at all, in the presence of congestive heart failure, fluid retention, and hypertension, as well as in patients with asthma, advanced kidney disease, and dehydration (Clemett & Goa, 2000).

The risks of taking ibuprofen include bleeding, anaphylaxis, and gastrointestinal discomfort. The one-time dose reduces the risk for the common adverse reactions seen with non-selective COX inhibitors. In a study by Dahl et al. (1995), ibuprofen was compared to a placebo in patients undergoing hip surgery and there was no significant difference in blood loss between groups.

The risks of taking rofecoxib include bleeding, anaphylaxis, and gastrointestinal discomfort. The risks of these adverse reactions occurring are significantly less than that of non-selective COX inhibitors (Bombardier et al., 2000). Reuben & Connelly (2000) found that there was no effect on platelet aggregation or bleeding time.

Mukherjee, Nissen, & Topol, (2001) reviewed four studies comparing rofecoxib, celecoxib and non-selective NSAIDS. They hypothesized that COX-2 inhibitors may potentially have antiatherogenic effects by inhibition of inflammation. They also suggested that COX-2 inhibitors, in contrast, may increase prothrombotic activity due to

decreased vasodilation and antiaggregatory prostacyclin production.

This review article (Mukherjee et al., 2001) found an increase in risk for cardiovascular events with rofecoxib as compared to naproxen. The cardiovascular risk was primarily identified in the Celecoxib Longterm Arthritis Safety Study (CLASS) (Silverstein et al., 2000) and the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial (Bombardier et al., 2000). The CLASS study found no significant difference in cardiovascular events in patients taking celecoxib versus non-selective NSAIDs. Patients in the CLASS study were allowed to continue to take aspirin for cardiovascular prophylaxis (< 325 mg). The VIGOR trial compared rofecoxib to naproxen in 8076 patients who were at least 50 years of age with rheumatoid arthritis. Patients were excluded if they were taking aspirin. In the VIGOR trial, four percent of the study subjects met the FDA's recommended criteria for aspirin therapy. These patients accounted for 38% of the cardiovascular events in the study. A total of 111 patients in the rofecoxib and 50 in the naproxen group had cardiovascular events. Excluding this population, there was no significant difference between rofecoxib and naproxen in the occurrence of cardiovascular events. As evidenced by the review of literature patients using aspirin for it's anti-platelet effects should be excluded from a study due to their increased risk of a cardiovascular event.

The next two studies compared rofecoxib and nabumetone versus a placebo (Mukherjee et al., 2001). Patients were allowed to continue to take low dose aspirin. Again, no significant difference was found in the incidence of cardiovascular events among the groups. These studies evaluated patients with chronic rheumatoid and

osteoarthritis. Rheumatoid arthritis increases the risk of myocardial infarction. In addition, the studies that allowed patients to continue low dose aspirin therapy did not show an increased risk for cardiovascular events. This suggests that selective COX-2 inhibitors do not increase the physiologic risk, nor do they offer cardiovascular protection by prevention of platelet aggregation. In addition, this data was in reference to patients who were taking NSAIDs continuously. There was no suggestion as to the effect of selective COX-2 inhibitors when used intermittently. Additional research needs to be done in this area to define the role that selective COX-2 inhibitors play in cardiovascular events.

COX-2 inhibitors are contraindicated in patients who have had asthma, urticaria, or other allergic-type reactions after taking aspirin or NSAIDs (Clemett & Goa, 2000; Noble et al., 2000). COX-2 inhibitors can cross the placenta and are contraindicated in women in the third trimester of pregnancy and lactating women. Celecoxib is contraindicated in patients with an allergy to sulfonamides; however, rofecoxib is not (Silverstein et al., 2000).

COX-2 inhibitors do not affect bleeding time, but may increase the prothrombin time in patients that take warfarin. Both NSAIDs and warfarin are extensively protein bound affecting the pharmacokinetics of warfarin. Patients who consume alcohol or have a preexisting coagulation disorder while taking a COX-2 inhibitor may also be at increased risk of bleeding (Noble et al., 2000).

Current COX-2 research has only been done on adults. Therefore, COX-2 inhibitors should not be given to patients less than 18 years of age until research has

demonstrated the safety of use for this group (Noble et al., 2000).

Total Abdominal Hysterectomy (TAH)

Hysterectomy is the second most common operation performed in the U.S. (65,000/year) (Margolis et al., 1999). The two approaches possible are vaginal and abdominal. The approach used is often decided in the operating room after a pelvic examination is done to determine the uterine size, degree of prolapse, and the presence of pelvic pathology (Margolis et al., 1999). Laparoscopy may be performed in order to evaluate the pelvis and free up adhesions, which would have made a vaginal approach unsafe. If the patient is over 45 years old, a bilateral salpingo-oophorectomy is also often performed as prophylaxis for ovarian cancer (Margolis et al., 1999).

Abdominal hysterectomy is often performed through a midline or a transverse incision, referred to as Pfannenstiel's incision. This incision can be improved with the Maylard step, where the rectus muscles are cut, or a Cherney rectus muscle detachment done at the pubic insertion (Margolis et al., 1999). A self-retaining retractor is placed. Then the round, ovarian, and broad ligaments are clamped, cut, and tied. Uterine vessels are identified and ligated. A bladder flap is created and the uterosacral and cardinal ligaments are cut and ligated. The cervix is removed and the vaginal cuff is closed using the uterosacral ligaments for support (Margolis et al., 1999). The abdominal approach is required when pelvic bony structure and uterine size do not accommodate the use of a vaginal approach. It is also required if there are extensive pelvic adhesions or gynecological cancers (Margolis et al., 1999).

Women requiring a hysterectomy often have a diagnosis of uterine myoma, pelvic

relaxation syndrome, pelvic pain due to endometriosis or adhesions, uncontrolled uterine bleeding/dysmenorrhea, endometrial hyperplasia, or gynecological cancers. Postoperative pain scores average 5-8 on a 0-10 scale for the abdominal approach and 4-6 for the vaginal approach (Margolis et al., 1999). Mortality for the abdominal approach ranges from 8.9/10,000 if the patient is < 25 years to 255.8/10,000 if the patient is >75 years. This is compared to the range of mortality for the vaginal approach: 0/10,000 if the patient is < 25 years to 56.8/10,000 if the patient is > 75 years (Margolis et al., 1999).

Carter, Ryoo & Katz (1994) compared laparoscopic-assisted vaginal hysterectomy to total abdominal hysterectomy. These researchers evaluated the length of operation, blood loss, length of hospital stay, drug requirements for pain, postoperative pain levels, and activity levels. Nineteen patients were included in each group (total abdominal hysterectomy or laparoscopic-assisted vaginal hysterectomy). They were matched for age, weight, diagnosis, and uterine weight. The average surgical time for the laparoscopic-assisted vaginal hysterectomy was 144 minutes and the total abdominal hysterectomy was 98 minutes, demonstrating a significant difference ($p < 0.005$). The researchers did not find significant differences between estimated blood loss and change in hemoglobin levels between the two groups. Although there was no significant difference in pain levels reported during hospitalization, the total abdominal hysterectomy group used an average of 436 mg (± 202) of meperidine as compared to the 197 mg (± 105) used by the laparoscopic-assisted vaginal hysterectomy group ($p < 0.005$). The length of stay was also significantly less for the laparoscopic-assisted group (2.125 days) as compared to the total abdominal hysterectomy group (3.542 days, $p <$

0.001). The level of activity was assessed using a 1-10 scale with 1 being extremely limited activity and 10 having no limits on activity. The laparoscopic-assisted vaginal hysterectomy group had an activity level of 9.2 by day 14 whereas the total abdominal hysterectomy group had only an activity level of 6.4 ($p < 0.005$). Randomization was not used in this study, nor did the investigators discuss reliability or validity of their measurement instruments.

As the above studies have shown, laparoscopic-assisted vaginal hysterectomies are a safe and effective alternative to total abdominal hysterectomy but as mentioned earlier many patient characteristics (pelvic structure, uterine size, cancer, and adhesions) may require an abdominal approach. A double-blinded study by Thompson et al., (2000) compared postoperative pain in two groups of total abdominal hysterectomy patients. The first group received meloxicam 15 mg rectally after induction of anesthesia and prior to the start of surgery. Meloxicam is an NSAID that is COX-2 selective. The second group received a placebo suppository in the same manner. All patients were placed on a morphine PCA pump postoperatively. Pain scores were assessed using a VAS 0-100 mm scale and PCA morphine consumption was assessed at 2, 4, 8, 12 and 24 hours after surgery. Researchers also recorded the incidence of nausea and degree of sedation. Again, reliability and validity were not reported for the instruments used. This study found that there was no significant difference between groups on the amount of morphine used at any time, however pain scores were significantly higher in the placebo group. Mean area under the curve pain scores at rest were 683 mm per hour in the placebo group and 367 mm per hour in the meloxicam group ($p < 0.005$). Pain scores were also

significantly less in the meloxicam group on movement ($p < 0.05$) and with coughing ($p < 0.05$).

Summary

Selective and non-selective NSAIDs are a heterogeneous group of medications that possess varying degrees of anti-inflammatory, analgesic, and antipyretic properties. NSAIDS also share several untoward side effects, the most common being gastrointestinal irritation. The development of selective COX-2 inhibitors provides similar efficacy compared to the non-selective NSAIDs, while preserving the protective prostaglandins produced by the COX-1 enzyme. Rofecoxib, a selective COX-2 inhibitor, is commonly used for osteoarthritis and postoperative pain. Rofecoxib has clinical efficacy comparable with high doses of ibuprofen and its duration of action is three-fold longer. Rofecoxib was found to be superior to celecoxib in overall analgesic effect, time of onset, peak effect, and duration. There is very little information available on the use of COX-2 inhibitors as modulators of preemptive analgesia in postoperative patients. There is a need to study the benefits of ibuprofen compared to rofecoxib in providing postoperative analgesia. Also the review of literature shows a need to assess pain, analgesic consumption, and incidence of side effects comparing rofecoxib, ibuprofen and placebo.

CHAPTER III

Methodology

A randomized, double-blinded, placebo-controlled clinical trial was conducted to determine if there is a difference between preemptive use of rofecoxib, ibuprofen, or placebo in the attenuation of postoperative pain. The characteristics of the study population, sample, setting, and instrumentation are discussed in this chapter. Additionally, this chapter describes the procedures for data collection, strategy for protection of human subjects, study design, budget, and time-line.

Population, Sample, and Setting

The setting for this study was a military medical center located in the state of Hawaii. The 256-bed medical facility provides care to active duty military members in the Army, Navy, Air Force, Marines, and Coast Guard, as well as their family members, retirees, and retiree family members. The tri-service medical facility is a major teaching center for the Army that provides graduate training in numerous health-related disciplines.

The subjects for this clinical trial were selected from a population of female patients scheduled for gynecological surgery with general anesthesia. Subjects were screened for possible exclusion criteria prior to enrollment (Appendix A). All subjects included in this study were between 18 and 80 years of age, physical status (PS) classification I or II as defined by the American Society of Anesthesiologists (ASA) (Role & Galloway, 2000), weighed at least 50 kilograms, and had a body mass index less than 35.

Review of the use of the NRS coupled with the personal experience of the investigators led to the prediction that 40 to 60% of patient ratings were found to cover a 2-point range on the 11-point scale (zero to ten). As a result, a 2-point difference

between the treatment group and the control group was used as the operational definition of a clinically meaningful difference in pain scores. This effect size was equated to a "moderate effect size" as defined by Paice and Cohen (1997) as an effect size of 0.80 standard deviations or larger.

Sample size was determined to be twenty subjects per group (placebo, ibuprofen, and refecoxib) for a total of 60 subjects. Each subject's pain score was measured at fifteen time points (at surgical admit, PACU admit, PACU discharge, and every four hours for 48 hours). The number of subjects was determined using a moderate effect size of 40%, when comparing an overall mean (e.g. total morphine administered), for each of the three groups with an alpha level of 0.05 giving a statistical power of 78%. A 45% or higher difference in rates of dichotomous data (e.g. yes/no emesis) was observed in order to detect a significant difference with a power of 73% at an alpha level of 0.05. In addition to the 60 subjects needed for data analysis, an additional 15 subjects were to be enrolled in order to accommodate a possible 25% attrition for a total of 75 patients.

Patients with an allergy to NSAIDs were excluded from this study. Other exclusion criteria, as identified by previous research studies (Bjarnason et al., 1997; Law et al., 2000), included coagulopathies, hepatic or renal disease, acute or chronic opioid use, psychotropic drug use, history of psychiatric or mood disorders, congestive heart failure, asthma, and lactating mothers. Patients taking any medications or substances that may interact with rofecoxib or ibuprofen were excluded from this study. In addition, those patients who have taken aspirin in the past 10 days or NSAIDs within the last 3 days were excluded. Furthermore, patients who were unable to communicate in English were excluded from the study.

All patients consenting to participate in the study, and meeting the selection criteria, were included in the study. Subjects were randomly assigned to the rofecoxib,

ibuprofen, or placebo group. Randomization was determined by the inpatient pharmacy using a computerized randomization table. Depending on the assigned group, patients received rofecoxib, ibuprofen, or a placebo from one of the primary investigators one hour prior to surgery.

Instrumentation

The instruments used to gather data during this study were an investigator-developed demographic worksheet and a pain assessment tool incorporating the NRS. The amount of pain medication given was also tracked (Appendix B).

Data collection worksheet.

Demographic data that was collected included age, height, weight, PS classification, time and date of last dose of NSAID/aspirin/opioid administration, ethnicity, present hormone therapy, surgical procedure, and the first day of the last menstrual cycle. The patient report of height and weight was converted to centimeters and kilograms, respectively.

Pain assessment tool.

As the nature of pain is subjective, assessment relies on information obtained from the patient. According to the pain guidelines established by the Agency for Health Care Policy and Research (1992), the patient's self report is the single-most reliable indicator of the existence of acute pain. The study participant's subjective assessment of pain was evaluated throughout the study period.

Several instruments have been developed to measure the intensity of pain. Selection of the proper tool was based on the Agency for Health Care Policy and Research (1992). The factors used included the psychometric evaluation, the necessary level of patient's cognitive abilities, the time and effort required to complete the tool, and the institution's guidelines.

The NRS is a self-report instrument that has been widely used to measure pain intensity in the clinical setting and in clinical research (Parker, Holtmann, Smith & White, 1994; Reuben, 2000). It was chosen as the pain intensity instrument to be used in this study. This instrument is currently used at TAMC and all nursing personnel are familiar with its use. It has been used successfully in past research at TAMC (Gibbons & Harm, 2000; Pitcher, 2001). In addition, it is simple to administer, interpret, and has been shown to be both valid and reliable. The NRS consists of a numerical scale, with the numbers at each end of the scale representing the extremes of subjective pain response. The numerical anchor of zero was accompanied by a verbal descriptor of "no pain", and the numerical anchor of 10 was accompanied by a verbal descriptor of "the worst pain you can possibly imagine." Patients may score their pain as any whole number within these anchors. We presented the instrument to the patients in verbal form and they rated their pain intensity by indicating a number that best corresponds to their current perception of pain sensation.

The validity of an instrument is the degree to which the instrument measures what it is intended to measure (Polit & Hungler, 1999). One method of determining validity is criterion-related validity. For this method, the researcher seeks to establish the degree of correlation between the scores of the instrument in question and some external criterion, usually an established instrument (Polit & Hungler, 1999). A study by Paice & Cohen (1997) supports criterion-related validity of the NRS. They asked 50 subjects with cancer to rate their pain on three pain intensity scales including the visual analog scale, simple descriptor scale, and the verbal NRS. The results of the data analysis demonstrated a significant correlation between the scores on the visual analog scale and the verbal NRS ($r = 0.847$, $p < 0.001$). The strong correlation between the NRS and VAS, which has already been established as a valid pain assessment tool, helps demonstrate the validity of

the NRS to accurately measure subjective pain.

Reliability is the consistency with which an instrument measures the attribute it is designed to measure (Polit & Hungler, 1999). Test-retest is a method of determining instrument reliability that looks at stability over time. Stability is the extent to which the same scores are obtained by the same patients measured at different time intervals (Polit & Hungler, 1999). Ferraz et al. (1990) used test-retest reliability to assess reliability of the visual analog scale, verbal rating scale, and the NRS. They assessed 66 literate and 25 illiterate patients with rheumatoid arthritis to rate their pain on the three scales. The scales were presented in random order. After their regular medical consultation, the patients were asked to complete the scales again. Data analysis indicated that the NRS had the highest reliability of the three tools. The Pearson product moment correlation between the first and second assessment was 0.96 for the NRS in the literate group and 0.95 in the illiterate group. The results of this study support the use of the NRS as a reliable instrument.

In addition to strong validity and reliability, the NRS has a number of other advantages including simplicity, ease of use, and ease of scoring (Flaherty, 1996). The verbal NRS minimizes unnecessary burdens or inconveniences placed on the patient in the immediate postoperative period. Patients in the immediate postoperative period may continue to experience the residual effects of anesthesia, such as drowsiness, blurred vision, or nausea making it difficult for them to complete a written scale (Paice & Cohen, 1997). This instrument also minimizes burdens placed on nursing staff by eliminating the time-consuming task of measuring the patient's written response, and thereby delaying the administration of analgesics. Because the NRS is used commonly in clinical practice at TAMC, additional personnel involved in the data collection were familiar with its use. These features made the verbal NRS an attractive instrument to use for our research

study.

Patients were taught to use this scale in the preoperative period. It was presented verbally to patients in the following manner: "On a scale of 0 to 10, with 0 equal to no pain and 10 equal to the worst pain you can possibly imagine, how much pain do you feel right now?" The Post Anesthesia Care Unit/Surgical Admission Center nurses were responsible for accurately recording the patient's response by circling the corresponding number on the pain assessment tool worksheet (Appendix C). Additionally, the nurses recorded the time, dosage, and name of the analgesic medication given between data collection points.

Procedure for Data Collection

All participants, anesthesia care providers, and nursing staff were given instructions on the study and the method of implementation prior to the beginning of the study. In order to reveal any weaknesses, flaws, or discrepancies in the design, a pilot study following study protocol was conducted using the first 10 patients. Data from the first 10 patients were analyzed to allow for further revisions of the study design. The procedure for data collection was as follows:

1. Potential candidates were identified and asked if they would be interested in participating in the study during their preoperative clinic interview.

2. If interested, each patient completed an exclusion criteria worksheet (Appendix A).

3. If the patient met the selection criteria, they were given an informed consent to read and sign.

4. The researcher was available to answer any questions or concerns that the patient had regarding the study.

5. The patient was enrolled in the study after granting her consent.

6. The day prior to the surgery, patients were called to remind them of the study and to answer any additional questions.

7. On the day of surgery, the pain assessment tool was presented to the patient for familiarization. The patient's baseline pain score was recorded in the surgical admission center preoperatively.

8. Approximately one hour prior to the surgical procedure, in a double-blinded fashion, patients received an oral dose of rofecoxib 50 mg, ibuprofen 400 mg, or placebo. The equivalency of ibuprofen 400 mg to rofecoxib 50 mg was determined by the inpatient pharmacy and by Malmstrom et al. (1999). All medications were prepared by the pharmacy. Additionally, they were all in elixir form, orange-colored, berry-flavored, and twenty milliliters in volume.

9. An intravenous (IV) catheter was placed in the subject's hand or arm and an infusion of lactated ringers was started.

10. Patients received 1-5 mg of midazolam, IV, as needed for anxiolysis.

11. The subjects were transported to the operating room for surgery.

12. The anesthetic agents were standardized for all participants.

Induction

1. Patients were positioned supine with the head elevated on a small pillow and extended slightly to facilitate airway management.

2. The anesthesia provider ensured that the patient had a patent intravenous infusion by inspecting the site after all patient movement was completed and by observing the rate of flow.

3. Patients were preoxygenated by breathing normally for 3-5 minutes at an oxygen flow rate of 6 liters/minute by mask placed over the patient's face.

4. Up to 5 mcg/kg of fentanyl, IV, was titrated prior to induction.

5. Anesthesia was induced with propofol 1.5-2.5 mg/kg, IV.

6. The ability to ventilate was tested by delivering a few positive pressure breaths.

7. When the ability to ventilate was established, rocuronium 0.6-1.2 mg/kg, IV, was administered for neuromuscular blockade.

8. Positive pressure ventilation was maintained while monitoring neuromuscular status with the peripheral nerve stimulator.

9. When twitch was absent, direct laryngoscopy was performed and the endotracheal tube was passed through the vocal cords. The centimeter marker on the tube was noted at the level of the upper incisors.

10. The cuff of the endotracheal tube was inflated.

11. The endotracheal tube was connected to the breathing circuit. Positive pressure ventilation was administered with 100% oxygen while confirmation of endotracheal tube placement was verified by chest rise and fall, mist in the endotracheal tube, appropriate end-tidal CO2, bilateral breath sounds, and absence of gastric breath sounds.

12. Isoflurane was administered up to 3% expired fraction.

13. The endotracheal tube was secured.

14. Vital signs were monitored and recorded throughout the intraoperative period.

Maintenance

1. Patients were maintained with isoflurane, 0-3% expired fraction, and fentanyl (0-5 mcg/kg/hr).

2. Oxygen and air were titrated to maintain oxygen saturation greater than 97%.

Emergence

1. Dolasetron 12.5 mg, IV, as a postoperative antiemetic was administered.

2. If reversal of the neuromuscular blockade was necessary, glycopyrrolate (0.01-

0.02 mg/kg) and neostigmine (0.04-0.08 mg/kg) was administered IV.

3. After meeting extubation criteria, (sustained tetany for 5 seconds, full train of four, sustained head lift, spontaneous ventilations with adequate respiratory rate and tidal volume, and stable vital signs) the endotracheal tube was removed and oxygen at 10 liters per minute was administered via facemask.

4. Upon completion of the procedure, the subject was transferred to the PACU for routine recovery.

Postoperative Data Collection

1. The investigators performed an initial assessment of the patient's pain intensity using the NRS prior to the administration of opioids.

2. The recovery room staff provided rescue pain medication (morphine sulfate) as needed per orders written by the anesthetist.

3. PACU staff documented patient complaints of nausea and vomiting. They also documented amount and type of antiemetic given.

4. Reassessment of the patient's pain intensity was performed prior to discharge from the PACU.

5. Amount and type of medication given were documented in addition to the NRS score.

6. The gynecological physician admitted most patients to the surgical ward with a morphine PCA at a prescribed rate of administration.

7. Surgical ward nurses assessed the patient's pain every four hours for the first 48 hours postoperatively, using the verbal NRS.

8. Surgical ward nurses documented the amount of morphine used every shift, as well as any other pain medication given for the first 48 hours postoperatively.

Protection of Human Subjects

This study proceeded after obtaining approval from the appropriate institutional review boards. After identifying potential candidates, they were approached in the preoperative clinic and asked if they were interested in participating in the study. If selection criteria were met, the patient was asked to complete an exclusion criteria worksheet and an informed consent form (Appendix C). The researcher was available to answer any questions and concerns that the patient may have regarding the study. Patients were enrolled in the study after granting their consent. Every subject was assigned an identification number for confidentiality during the period of data collection and analysis. However, it was necessary to obtain social security numbers and home addresses of each subject in the event that the code needs to be broken for identification and notification of those who may have been adversely affected by the study. The procedure and maintenance of confidentiality were discussed with each subject.

Information gained from this study may be published in the medical literature but participants will not be personally identified. Subjects were informed that their decision to participate, or refusal to do so, would not affect the quality of their anesthesia care during or after surgery. Subjects were also informed that they had the right to withdraw from the study at any time.

The Institutional Review Board at TAMC agreed that the inclusion of a placebo group is ethical in this trial. Preemptive analgesia is not a standard of care at our institution. A review of the literature has revealed mixed results from the use of preemptive analgesia. Some studies suggest the positive effects of preemptive analgesia (Dahl et al., 1995; Dionne et al., 1983; Law et al., 2000) while others suggest there is no benefit (Huang et al., 2001; Owen et al., 1986). We believe that this supports our decision to include a placebo as a negative control group in our study.

Study Design

This study followed a randomized, double-blinded, placebo-controlled, clinical design. Both the researchers and study participants were blinded as to what treatment was administered. The double-blind method helped to minimize potential biases and prejudices of the researchers and subjects.

This study was a clinical trial conducted within a hospital setting. All subjects were selected from a convenience sample. The convenience sample consisted of all patients presenting for gynecological surgery at TAMC. The pharmacy randomly assigned subjects to a treatment group using a computerized randomization table. Medications were numerically pre-coded by the pharmacy. The numerical code of the medication was recorded on the data collection worksheet at the time of medication administration.

Procedure for Data Analysis

The statistical test used for data analysis of the NRS pain intensity scores was a two-way ANOVA with repeated measures over time. This test was utilized to determine whether there were significant differences in pain intensity within and/or between groups over time. A significant difference between groups would suggest that one medication was more effective at attenuating postoperative pain as compared to the others. The study design, with randomization into the treatment groups and interval-level data, allowed the to use of a parametric test. Additionally, the assumption was made that this population follows a normal Guassian distribution.

There were 15 data collection points measuring pain for each group. The first collection point was in the surgical admission center, the second and third points were upon admission and discharge from the PACU, respectively. The last 12 data collection points were taken every four hours for 48 hours postoperatively. In the case where a

single four-hour pain assessment was not recorded, a score was documented by averaging all scores over time and between groups. If more than four pain scores were not recorded, the patient's data was excluded from the study.

The statistical method used to analyze postoperative morphine consumption was a one-way ANOVA. This test was utilized to determine whether there were significant differences in morphine consumption between groups. A significant difference between groups would suggest that one medication was more effective at attenuating postoperative pain.

Morphine consumption was tracked using six data collection points for each group. The collection points coincided with the surgical ward's protocol, which requires documentation of morphine consumption at the end of each eight-hour shift (0600, 1400, and 2200 hours). The first data collection point included morphine administered in the PACU. Due to variable times of admission to the surgical ward, the first and last data collection points may have been less than eight hours. If the surgical ward nursing staff missed a data collection point, consumption data was retrieved through an audit of the PCA pump's history and the controlled substances inventory worksheet. All other narcotic analgesics were converted to morphine equivalents using the table by Ferrante and VadeBoncouer (1993). The total narcotic was evaluated using a one-way ANOVA.

Demographic variables including age, height, weight, body mass index, procedure, physical status classification, and ethnicity were collected and analyzed using a one-way ANOVA for interval data and a chi-square test for nominal data to determine whether the random assignment was effective in producing equivalent groups. A significant difference would require that any subsequent analysis take into account any confounding variables.

CHAPTER IV

Analysis of the Data

The purpose of this study was to evaluate the effect of the preoperative administration of rofecoxib 50 mg, ibuprofen 400 mg, and placebo on postoperative pain relief following gynecological surgery involving lower abdominal incision. This chapter compares the demographic characteristics and research findings of the three groups. This study contained two research questions: (a) Is there a difference between preemptive administration of rofecoxib, ibuprofen, and placebo in the attenuation of postoperative pain in females undergoing gynecological surgery involving a lower abdominal incision? (b) Is there a difference in the analgesic medication required postoperatively in females undergoing gynecological surgery involving a lower abdominal incision?

Description of the Sample

Seventy-one patients presented for gynecological surgery and met surgical criteria. Thirty-six were subsequently enrolled into the study. Two subjects were disenrolled, accounting for a 5% attrition rate. Reasons for attrition included: (a) the surgical technique was changed intraoperatively on one subject and (b) the other subject was removed from the study due to a change in anesthetic technique. There was one complication during the course of the study in which a patient had an allergic reaction to morphine. The patient was subsequently placed on a meperidine PCA without further incident. This patient remained in the study. The meperidine dosages were converted to morphine equivalents (Ferrante, 1993).

Twenty-eight subjects were not enrolled in the study due to exclusion criteria (Table 1). Most of the subjects were not enrolled due to asthma, morbid obesity, or allergy to NSAIDs. Six subjects requested epidurals. An additional 12 patients refused enrollment into the study (Table 1).

Table 1

Patients not enrolled in study (40)

Exclusion Criteria for Patients Not Enrolled in Study	Frequency
Patient refusals	12
History of asthma	7
BMI > 35	7
Requested regional technique	6
Psychiatric illness	3
Chronic pain medications	3
Gastric disorders	3
Allergy to NSAIDs	2
Does not understand English	2
Physical status classification	2
Coronary artery disease	1
Total	48

Note. Some patients may have been included in more than one exclusion category.

Subjects were randomized to one of the three treatment groups by the pharmacy using a computerized randomization table. Group I received oral rofecoxib 50 mg, group

II received oral ibuprofen 400 mg, and group III received oral placebo. Investigators, participants, and medical staff involved in the data collection were blinded to the study medication given to the subjects.

Demographic data was analyzed using descriptive statistics. A Chi-square test was used to measure the differences between groups regarding ethnicity, PS classification, and hormone therapy. A one-way ANOVA was used to measure the differences between groups regarding height, weight, age, and body mass index (BMI). The analyses showed no significant differences between groups in any demographic category.

A two-way ANOVA with repeated measures over time was used to analyze pain scores. A one-way ANOVA was used to compare the average total morphine consumption. A chi-square test was used to compare incidences of emesis between the three groups. These data were analyzed to determine if there was a significant difference in incidence of nausea and vomiting between groups and if this was associated with an opioid-sparing effect of the study medication.

Demographic data was compared between the three groups looking for homogeneity of characteristics to include age, height, weight, body mass index, surgical procedure, physical status classification, ethnicity, and hormone therapy (Table 2). There were no statistically significant differences in the means between groups in regards to demographic data demonstrating that the groups were similar on these variables. In addition, the proportion of ethnic patients enrolled reflected the TAMC population. The Caucasian group had 14 subjects, the African-American group had 15, and the Hispanic, Pacific Islander, and Asian group had 7.

Table 2

Demographic Data Comparing the Three Groups (N = 36)

Demographic Data	Group I (n = 14)	Group II (n = 11)	Group III (n = 11)	Probability
Age (years)	36.43 (1.92)	37.91 (2.01)	34.00 (2.11)	0.42
Height (cm)	154.21 (7.31)	160.46 (2.39)	160.76 (1.83)	0.59
Weight (kg)	81.31 (30.07)	69.91 (10.81)	66.27 (11.77)	0.18
Body Mass Index	25.93 (4.46)	27.10 (4.72)	25.50 (3.70)	0.66
Ethnicity				
Caucasian	6 (17%)	4 (11%)	4 (11%)	N/A
African-American	5 (14%)	5 (14%)	5 (14%)	N/A
Hispanic	0 (0%)	0 (0%)	1 (3%)	N/A
Pacific-Islander	2 (6%)	1 (3%)	0 (0%)	N/A
Asian	1 (3%)	1 (3%)	1 (3%)	N/A
PS Classification				
I	7 (19.4%)	2 (5.6%)	5 (13.9%)	N/A
II	7 (19.4%)	9 (25.0%)	6 (16.7%)	N/A
Hormone				
Yes	1 (2.8%)	0 (0.0%)	1 (2.8%)	N/A
No	13 (36.1%)	11 (30.6%)	10 (27.8%)	N/A

Note. Values for continuous data are mean plus or minus one standard deviation. The numbers are frequencies referring to the actual subjects.

When comparing types of surgical procedures there were no differences between groups (Table 3). There were also no statistically significant differences in the amount of propofol, fentanyl, rocuronium, isoflurane, neostigmine, and glycopyrrolate given. This indicates strict adherence to the established anesthetic protocol. In addition, no

statistical significant difference existed in total surgery time, total PACU time, or length of hospital stay.

Table 3

Surgical Procedure and Anesthetic Variable (N=36)

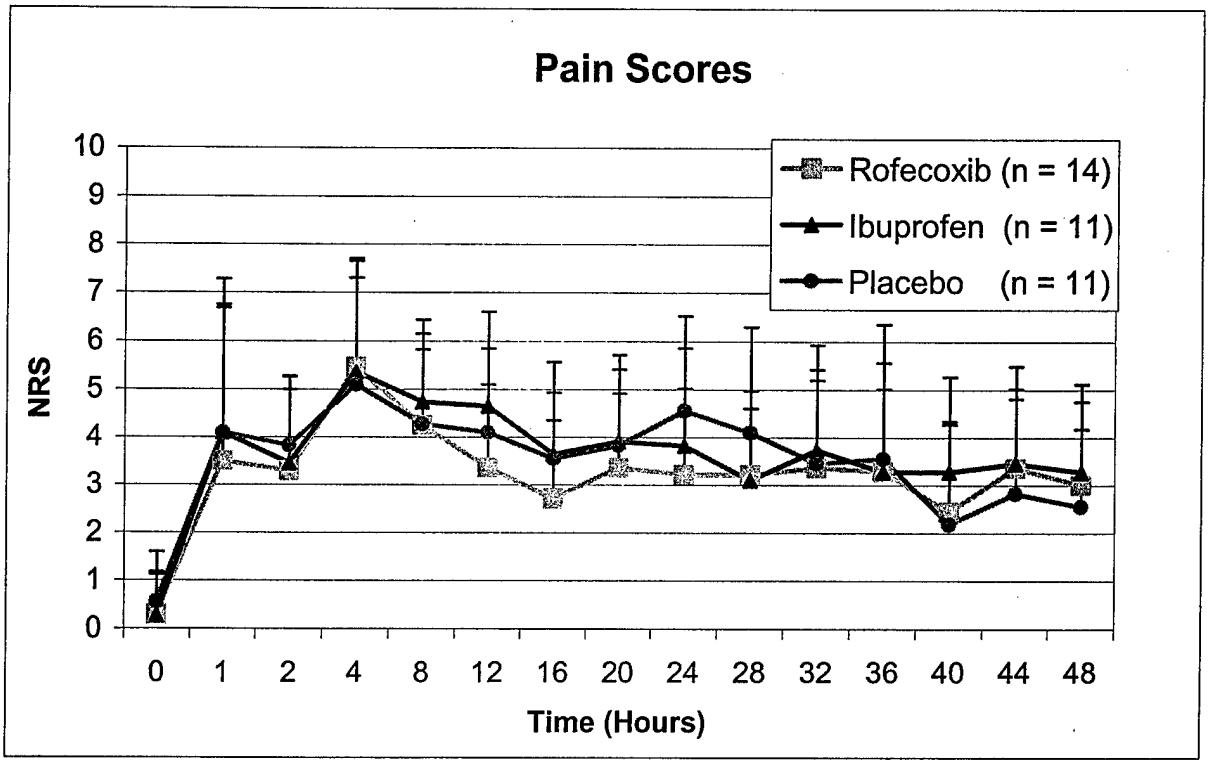
Variables	Group I (n = 14)	Group II (n = 11)	Group III (n = 11)	Probability
Surgical Procedure				
TAH	8 (22.2%)	7 (19.4%)	6 (16.6%)	0.71
Myomectomy	1 (2.8%)	1 (2.8%)	2 (5.6%)	0.71
MTA	2 (5.6%)	3 (8.3%)	2 (5.6%)	0.71
Cystectomy	1 (2.8%)	0 (0.0%)	1 (2.8%)	0.71
Laparotomy	2 (5.6%)	0 (0.0%)	0 (0.0%)	0.71
Total surgery time (min)	167.36 ± 70.07	176.55 ± 65.97	154.27 ± 58.07	0.27
Total PACU time (min)	97.64 ± 32.29	97.46 ± 36.14	100.73 ± 39.62	0.97
Length of hospital Stay (hrs)	46.98 ± 15.83	54.55 ± 26.63	49.77 ± 15.96	0.64

Note. Values for continuous data are means plus or minus one standard deviation.

Findings

Data Analysis

The first research question is as follows: Is there a difference between preemptive administration of rofecoxib, ibuprofen, and placebo in the attenuation of postoperative pain in females undergoing gynecological surgery involving lower abdominal incision? The NRS was used to evaluate postoperative pain scores. Pain was assessed at 15 time intervals: (a) preoperative pain score (baseline), (b) PACU admit, (c) PACU discharge, and (d) every 4 hours for 48 hours on the hospital ward 5B1. This data was analyzed using a two-way ANOVA with repeated measures over time. The findings showed that



there was no significant difference between groups in the attenuation of postoperative pain following gynecological surgery ($p = 0.65$) (Figure 3).

Figure 3. Comparison of Postoperative Pain Scores
1 = preoperative score, 2 = PACU admit score, 3 = PACU discharge score, and 4-15 = every four hours postoperatively on the ward.

The second research question is as follows: Is there a difference in the analgesic medication required postoperatively in females undergoing gynecological surgery involving a lower abdominal incision? Total morphine consumption was calculated over the 48-hour postoperative period. Medications given in addition to, or in replacement of, morphine during the 48-hour postoperative period were converted to morphine equivalents. Parenteral morphine 10 mg, oral oxycodone (opioid agonist contained in Roxicet®) 30 mg, parenteral meperidine 75 mg, oral codeine 200mg, and parenteral fentanyl 100 mcg are considered equianalgesic doses (Ferrante, 1993). The mean

morphine equivalent consumption for the three groups was: group 1) 56.08 mg, +/- 30.12 mg, group 2) 65.90mg, +/- 42.53 mg, and group 3) 69.35 mg, +/- 40.66 mg. This data was analyzed using a one-way ANOVA. The findings showed that there was no significant difference in analgesic consumption between groups in the 48-hour postoperative period ($p = 0.65$) (Figure 4).

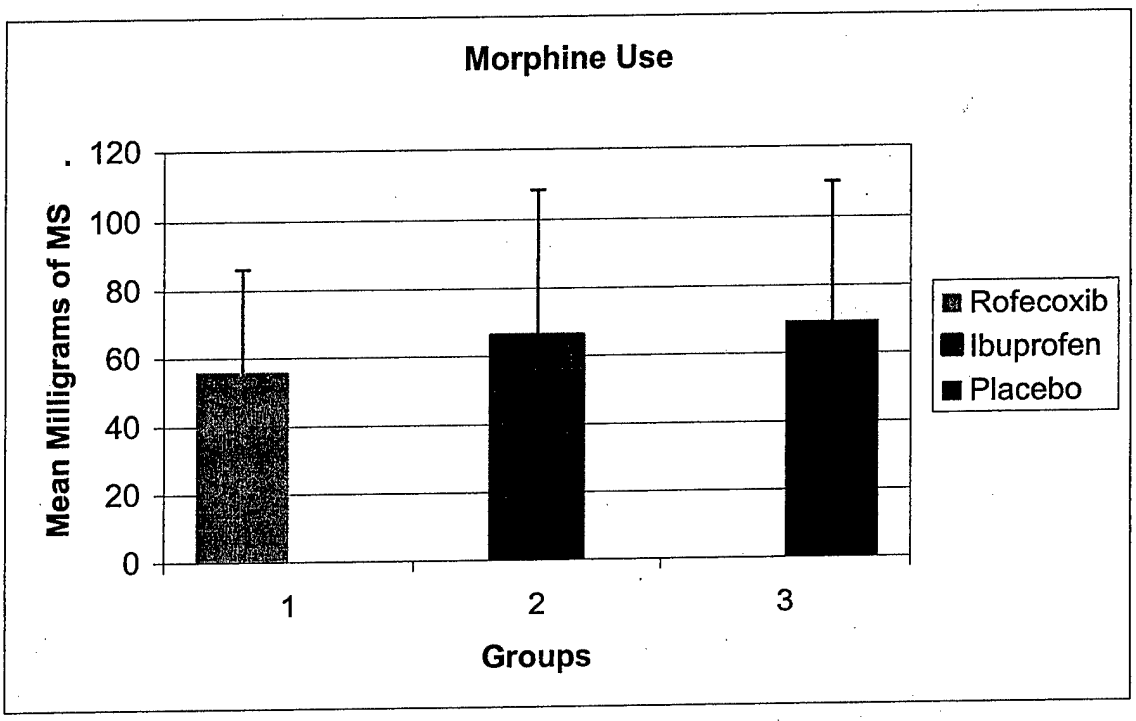


Figure 4. Comparison of Postoperative Analgesic Consumption

However, there was an important finding when combining the ethnicities of groups 3, 4, and 5 (Hispanic, Pacific-Islander, and Asian) and comparing them to group 1 (Caucasian) and group 2 (African-American) in regards to morphine equivalents. Using the ANOVA the findings showed a difference existed between ethnic groups in relation to postoperative analgesic requirements. Post-hoc analysis was conducted utilizing a

Tukey-Kramer test and it determined which groups were significant. When analyzing the post hoc contrasts, the Hispanics, Pacific Islanders, and Asians together required less postoperative analgesic medications when compared to Caucasians ($p = 0.011$) or African-Americans ($p = 0.027$).

A Chi-square test was used to analyze the incidence of nausea and vomiting between groups. PACU nurses documented either a "yes", indicating an incidence of nausea or vomiting or a "no" indicating a lack of occurence. The analysis showed no significant difference between groups. Eleven patients experienced nausea, four from group 1, two from group 2, and five from group 3. They were treated with ondansetron 4 mg intravenously.

Summary

This prospective, double-blinded, randomized, placebo-controlled pilot study analyzed the effects on postoperative pain and analgesic consumption when subjects were given rofecoxib, ibuprofen, or placebo prior to gynecological surgery requiring lower abdominal incision. There were no significant differences in pain scores, morphine consumption, or demographics between the three groups. However, the results showed Hispanic, Pacific Islander, and Asians required significantly less postoperative analgesic medications than Caucasians or African-Americans. Also, data analysis suggested a trend in the rofecoxib group consuming less postoperative morphine.

CHAPTER V

Discussion, Conclusions, Implications, and Recommendations

Uncontrolled postoperative pain can be severe enough to warrant unplanned hospital admissions. Additionally, postoperative pain can lead to decreased patient satisfaction and delayed recovery times. The goal of this study was to test the theory of preemptive analgesia, or attempting to prevent pain before it occurs.

Preemptive analgesia is an attempt to attenuate pain pharmacologically prior to surgical tissue trauma. The NSAIDs, given preoperatively, inhibit prostaglandin synthesis and the resultant inflammatory response leading to the wind-up phenomena (Cousins & Power, 1999).

Preemptive analgesia studies have mixed results when studied in dental pain (Law et al., 2000) and gynecological surgery (Gibbons & Harm, 2000; Pitcher, 2001) models. This study was designed to determine whether there was a difference in postoperative pain scores and analgesic consumption in females receiving rofecoxib, ibuprofen, or placebo, preemptively, prior to undergoing gynecological surgery involving a lower abdominal incision. This chapter includes a discussion of the research findings, followed by conclusions, implications for nursing, and recommendations for further research.

Discussion

The research questions were designed to determine whether there was a difference in pain scores and/or morphine consumption in patients that received either rofecoxib 50 mg, ibuprofen 400 mg, or placebo, one hour prior to surgical incision.

The study was designed to minimize extraneous variables by (a) using a standardized preoperative sequence and study drug administration times, (b) using a standardized induction sequence, (c) no oral gastric tube to withdraw residual study drug, (d) standardized intraoperative anesthetic maintenance plan, (e) standardized postoperative analgesic and antiemetic protocols, and (f) standardized types of surgeries/incisions.

Our study results demonstrated no significant differences in pain scores or morphine consumption postoperatively. These findings were inconsistent with a study conducted by Dionne et al. (1983) in which 107 dental outpatients were randomized between four treatment groups, (a) ibuprofen preoperatively and postoperatively, (b) acetaminophen preoperatively and postoperatively, (c) placebo preoperatively and acetaminophen and codeine postoperatively, and (d) placebo preoperatively and postoperatively. These authors reported significantly less postoperative pain in the ibuprofen group than the other groups. Explanations for this difference may be that they administered additional NSAIDs postoperatively as opposed to our single preoperative dosing regimen. Another difference may be that they used different medications and doses than we used in our study.

The results of our study did not correlate with those of a previous study conducted at our institution. Gibbons and Harm (2000) compared the preemptive effects of ibuprofen and ketorolac in patients undergoing laparoscopic bilateral tubal ligations. They found that the ibuprofen 800 mg group had lower NRS scores ($p < 0.01$) compared to the ketorolac 30 mg group. This decrease in pain scores was seen from two hours postoperatively until bedtime. Our study did not show a significant decrease in

postoperative pain scores in the ibuprofen, rofecoxib, or placebo groups. A possible explanation for this may be a difference in dosing. Gibbons and Harm used 800 mg of ibuprofen as opposed to use of a 400 mg dose in this study. Additional explanations for the difference in results may be due to the difference in types of surgeries.

Valdecoxib, a relatively new COX-2 inhibitor that has been used both orally and intravenously overseas, has recently undergone studies. Results have found that valdecoxib provides significantly greater pain relief from 6 to 24 hours as compared to oxycodone 10 mg/acetaminophen 1000 mg (Reynolds, Recker, Hubbard, North, & Verberg, 2002). Valdecoxib's prolonged duration of action makes it ideally suited for use in providing preemptive analgesia. Additionally, valdecoxib has a median peak onset of action of 30 minutes when taken orally (Reynolds et al., 2002). In contrast, rofecoxib has a peak onset time of 45 minutes.

A recent study explored the preemptive analgesic effects of valdecoxib in patients undergoing orthopedic foot surgery (Daniels, Paul, Hubbard, Recker, Verburg, 2002). Daniels et al. used a single oral dose of valdecoxib 20 mg, 40 mg, 80 mg, or placebo. They found that the 40 mg and 80 mg had a statistically significant prolongation in the time to rescue medication administration. The mean time to rescue medications in the 40 mg and 80 mg groups were 483 and 485 minutes respectively. Time to rescue medication for the 20 mg and placebo groups were 424 and 204 minutes respectively. In contrast to This study's results, valdecoxib appears to be an effective preemptive analgesic when given as a single dose. Although the results of the Daniels et al. study are promising, further research is warranted.

The degree of pain elicited by orthopedic procedures is different from pain of a more visceral nature, such as in procedures involving the abdominal cavity (Aida et al., 1999). A repetition of this study in patients undergoing abdominal procedures could be the next step. This type of study population is often not able or allowed to have anything by mouth for a variable period of time postoperatively. These patients may not be able to take oral medications for 12-24 hours after surgery. A solution to this problem would be the parenteral formulation of valdecoxib. Although not yet approved by the FDA for use in the U.S., this formulation does exist and is currently undergoing testing.

Another study tested the opioid sparing effectiveness and analgesic efficacy of valdecoxib (Camu, Beecher, Recker, & Verburg, 2002). The study population was patients undergoing total hip arthroplasty. Groups received 20 mg, 40 mg, or placebo, beginning 1 to 3 hours prior to surgery and continued twice a day throughout the course of the study. These researchers found a 40% decrease in postoperative morphine consumption compared to the placebo group (Camu et al., 2002). The study design incorporated the use of a preemptive dose of valdecoxib as well as continued administration of this drug in order to maintain a serum level high enough to affect a significant decrease in morphine consumption. This raises some questions as to whether a single dose administration of rofecoxib in this pilot study was enough to significantly decrease postoperative pain and morphine consumption.

Limitations

This study had several limitations that affect the conclusions that could be made. One limitation is that only a single dose of medication was given prior to surgery. In order to

get to a steady state, or therapeutic blood concentration, five doses would have needed to be administered. It might have been advantageous to administer more than one dose of study medication preoperatively.

A second limitation is that the medication was given one hour immediately prior to surgery. Patients that are anxious may have decreased gastric motility and probably had varying rates of medication absorption. To attempt to overcome this limitation, and to promote absorption the medications were given in an elixir form. Additionally, it may have been beneficial to give the medication earlier on the day of surgery to ensure medication absorption.

Another limitation is the small size of the study population. After enrollment of patients was started, there were several extended time periods where the gynecological service was not performing the types of surgeries that were to be included in this study. Additionally, more patients than anticipated chose not to participate in this study. Another reason why enrollment was less than anticipated is that numerous patients were excluded for safety reasons. Due to these factors, the desired number of patients were not enrolled. This was the reason the study was changed to a pilot study.

Conclusions

The following conclusions were drawn based on the analysis of data.

1. No significant difference was found between treatment groups in the attenuation of postoperative pain.

2. No significant differences were found between treatment groups in postoperative analgesic consumption.

3. No significant differences were found between treatment groups in the incidence of postoperative nausea.

4. A significant difference was found in postoperative pain scores when comparing certain ethnicities. When grouped together, Hispanics, Asians, and Pacific Islanders had significantly lower pain scores that Caucasians ($p = 0.011$) and African-Americans ($p = 0.027$). Caucasian and African-American scores were not significantly different from each other.

Implications for Nursing

One key point noted in this study was the fact that patient's average reported pain scores were between 3 and 4 out of 10 at most time points. The policy at this institution is to consider treating any pain that is greater than 3 out of 10 (TAMC OP 357, 1997). Patients typically receive detailed education on their PCA in the early postoperative period when they may still be under the effects of the anesthetic agents they received intraoperatively. Nurses need to ensure that patients have a good understanding of how to effectively treat their pain using a PCA.

A post-hoc analysis of these data showed significantly higher pain scores reported by Caucasians and African-Americans when compared to Hispanics, Asians, and Pacific-Islanders when grouped together. While further investigation is warranted, this finding may provide nurses with more insight into the pain management practices of patients of certain ethnicities. The utility of this information is that nurses can explore their patient's pain management beliefs when they assess their patients and find that they are currently experiencing pain levels greater than three out of ten.

Throughout the course of this study, the surgeons and ward nursing staff expressed varying perceptions of the patients' pain. At least one surgeon was noted to say that the study patients had more postoperative pain than non-study patients undergoing the same surgical procedure. This was an interesting observation in that study participants were placed on morphine PCAs postoperatively and theoretically they would self-administer analgesic according to their level of pain. Therefore, this emphasizes that Provider's perceptions should not be the guide for treatment of patients' pain and it is an opportunity for provider education.

Recommendations for Further Research

This study evaluated the effects of preemptive administration of ibuprofen, rofecoxib, and placebo in attenuating postoperative pain. While not statistically significant, patients that received rofecoxib (56.08, +/- 30.12) consumed less total morphine ($p = 0.78$) postoperatively than did those patients receiving either ibuprofen (65.90, +/- 42.53) or placebo (69.35, +/- 40.66). While also not statistically significant, PACU admit and discharge pain scores were lower for the rofecoxib group. Mean pain scores, with standard deviations are as follows: rofecoxib admit (3.5, +/- 3.25), discharge (3.29, +/- 1.98); ibuprofen admit (4.09, +/- 2.59), discharge (3.45, +/- 1.81); placebo admit (4.09, +/- 3.18), discharge (3.82, +/- 1.17). At the time these results were calculated the study only included 36 participants. It is unknown if the treatment was strong enough to have demonstrated a difference even if a larger number of subjects had been enrolled.

It is recommended that a follow-on study, or possibly a meta-analysis be done to determine if a larger sample size would result in statistically significant differences between groups. Another recommendation would be to consider administering the medication for two to three days before surgery in order to determine if further prostaglandin inhibition would yield different results. Additionally, incorporating additional doses of study medications postoperatively into the study design may prove to be more effective in decreasing postoperative morphine consumption.

Summary

This prospective, randomized, double-blinded, placebo controlled clinical trial studied the postoperative pain effects and postoperative morphine consumption of female PS classification I/II patients undergoing gynecological surgery involving a lower abdominal incision. A total of 36 patients were randomized between the rofecoxib, ibuprofen, and placebo groups. None of the groups reported significantly lower postoperative pain scores, or consumed significantly less postoperative morphine than the other groups. Additionally, there were no significant differences in postoperative nausea between the groups.

Based on the results of this study, additional areas that could be considered for further research were recommended. Also, elaboration on findings that may be of interest to practicing nurses was made.

APPENDIX A

Exclusion Criteria Worksheet

Patient's Home Phone Number: _____

Exclusion Criteria Worksheet for Total Abdominal Hysterectomy Study

Instruction: Please answer the questions below, if you answer yes to any of the questions below, Stop! Do not go on to the next question. If you have any questions or do not understand a question, please notify the researcher for assistance.

Patient ID # _____

1.	Do you have any problems understanding English?	Yes	No
2.	Are you less than 18 year or greater than 80 years of age?	Yes	No
3.	Do you weigh less than 110 pounds?	Yes	No
4.	Are you receiving an epidural or spinal for surgery?	Yes	No
5.	Are you allergic to NSAIDs or Aspirin? (ex. Motrin, Advil, Aleve)?	Yes	No
6.	Do you have asthma?	Yes	No
7.	Do you have any liver problems?	Yes	No
8.	Do you have any kidney problems?	Yes	No
9.	Do you have ulcers or bleeding in your stomach?	Yes	No
10.	Have you taken aspirin within the past 10 days?	Yes	No
11.	Have you taken NSAIDs within the last 3 days?	Yes	No
12.	Do you have any psychiatric illnesses?	Yes	No
13.	Are you currently on any pain medication? (ex. Morphine, Percocet, etc.)	Yes	No
14.	Are you currently breast-feeding?	Yes	No

APPENDIX B

Data Collection Worksheet

DEMOGRAPHIC DATA:

Name:_____ID#_____Date of Surgery:_____

Age_____ Height_____cm Weight_____kg BMI_____kg/m^2

Surgical procedure_____

PS classification_____Ethnicity_____

Hormone therapy: drug_____First day of last menstrual cycle_____

SURGICAL ADMISSION CENTER:

Time of medication administration_____

Medication identification number_____

Preoperative pain score 0 1 2 3 4 5 6 7 8 9 10

INTRAOPERATIVE DATA:

Time of induction:_____ Time of incision:_____

Duration of surgery:_____ Type of incision_____

Total opioid given (drug/dose)_____mcg

Total anxiolytic given (drug/dose)_____mg

POST-ANESTHESIA CARE UNIT:

Time of arrival_____Time of discharge_____

PACU admit pain score: 0 1 2 3 4 5 6 7 8 9 10

PACU discharge pain score: 0 1 2 3 4 5 6 7 8 9 10

Total morphine administered:_____mg

Other analgesics administered (drug / dose):_____mg

Total meperidine administered (for shivering)_____mg

Patient report of nausea? Yes / No Emesis? Yes / No

Antiemetic administration (drug / dose):_____mg

Number of times antiemetic administered_____

<u>SURGICAL WARD:</u>

Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10
Q4h pain score: time___________	0	1	2	3	4	5	6	7	8	9	10

Q8h PCA morphine totals:___________mg or Roxicet (# of capsules)___________

Q8h PCA morphine totals:___________mg or Roxicet (# of capsules)___________

Q8h PCA morphine totals:___________mg or Roxicet (# of capsules)___________

Q8h PCA morphine totals:___________mg or Roxicet (# of capsules)___________

Q8h PCA morphine totals:___________mg or Roxicet (# of capsules)___________

Q8h PCA morphine totals:___________mg or Roxicet (# of capsules)___________

Antiemetic administered (drug / dose):_______________________________mg

Antiemetic administered (drug / dose):_______________________________mg

Length of stay:_______________hrs

Perioperative Complications:

APPENDIX C

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 purposes.

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, adjudication of claims, and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State and local agencies.

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

PART A(1) - VOLUNTEER AFFIDAVIT

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/give consent as legal

representative for ______________________________ to participate in an investigational study entitled

"A Comparison of Preemptive Administration of Ibuprofen, Rofecoxib, and Placebo in Attenuation of Postoperative Pain Following Gynecological Surgery"

(Research Study)

under the direction of CPT Elizabeth K. Pulatie, AN

conducted at Tripler Army Medical Center

(Name of Institution)

The implications of my voluntary participation/consent as legal representative; 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/the rights of the person I represent on study-related injury, I may contact

the Center Judge Advocate

at Tripler Army Medical Center, Tripler AMC, HI 96859-5000 (808) 433-5311

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

I understand that I may at any time during the course of this study revoke my consent and withdraw/have the person I represent withdrawn from the study without further penalty or loss of benefits; however, I/the person I represent 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/the person I represent's health and well-being. My/the person I represent's refusal to participate will involve no penalty or loss of benefits to which I am/the person I represent is otherwise entitled.

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

I, ______________________________ SSN ______________________

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

______________________________ to participate in an investigational study entitled

____

(Research Study)

____

under the direction of ______________________________

conducted at ______________________________

(Name of Institution)

(Continue on Reverse)

A PHOTOCOPY OF THIS FORM MUST BE SIGNED BY ALL VOLUNTEERS.
Approved by the TAMC HUC/IRB on 22 Oct 2001 for TAMC# 44 08

PART A (2) - ASSENT VOLUNTEER AFFIDAVIT *(MINOR CHILD) (Cont'd.)*

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 I may contact

_____

at _____

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

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

_____

PART B - TO BE COMPLETED BY INVESTIGATOR

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

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

NATURE OF STUDY: You have been invited to participate in this study because you are scheduled to have a surgical operation to the lower abdomen. Control of post-operative pain is a major goal for your anesthesia care provider. Previous studies have suggested that giving medication before you have the surgery may reduce your pain post-operatively. This is referred to as pre-emptive pain control. The purpose of this study is to gather more information on pre-emptive pain control. This study involves giving one of two pain medications (rofecoxib or ibuprofen) or a placebo (a pill containing no medication) before surgery to evaluate how effective the medications are in reducing pain after surgery.

EXPECTED DURATION OF SUBJECT'S PARTICIPATION: Your participation in this study begins one-hour prior to surgery and ends 48 hours after being discharged from the recovery room.

WHAT WILL BE DONE: If you decide to take part in this study, you will receive one of the three treatment options (rofecoxib, ibuprofen or placebo) on the day of your surgery approximately one hour prior to the operation. By a random process (by chance, similar to flipping a coin), you will receive one of the three treatment options. Your chances of receiving any one of the three treatments are equal. This study involves random assignment because it is not clear at the present time if medication given pre-operatively is effective in reducing pain after the

Witness' Initials _____ Patient's Initials _____

surgery. For this reason, the therapy that is offered to you will be based upon a method of selection called randomization. Randomization means that your anesthesia care provider will call Pharmacy and the staff in Pharmacy will assign you to one of the three options. Neither you nor anesthesia care provider will know which treatment you have received. This method, called double-blinded, prevents you from being influenced by factors other than the medication in determining your level of pain. The rest of your care will remain the same. Your post-operative pain will be treated with pain medications as needed and ordered by your physician. Your comfort level will be measured postoperatively and how much medication you require after surgery will be monitored and recorded.

REASONABLY FORESEEABLE RISKS OR DISCOMFORTS: Rofecoxib and ibuprofen are both used for pain relief and both carry with them associated risks. These risks (usually minimal) include kidney dysfunction, bruising, bleeding from the surgical incision site, fluid retention, somnolence, dizziness, headache, gastrointestinal ulceration, and hypersensitivity reactions (unlikely in most people). Rofecoxib is a more selective drug than ibuprofen (nonsteroidal anti-inflammatory drug) thereby reducing some of the risks associated with ibuprofen use. To reduce your risks in this study, you will be closely screened for any contraindications for receiving the study medications as part of the pre-surgical assessment and evaluation and the completion of the exclusion criteria worksheet.

COMPENSATION FOR INJURY: Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. This is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

BENEFIT(S) TO THE SUBJECT OR TO OTHERS: A possible benefit would be that you would experience less pain after surgery because of the medication you received before the operation. Participation in this study, however, does not guarantee that you will not have pain after surgery. You will not be paid for participating in this study.

ALTERNATIVE PROCEDURES OR COURSES OF TREATMENT: If you decide not to participate in this study, other therapies will be used to reduce your level of pain post-operatively. These treatments will be provided to you after surgery. You will receive the same standard of care regardless of participation in this study. If you elect not to participate, you will simply not receive the study medication prior to surgery.

CONFIDENTIALITY: Information gained because of your participation in this study may be publicized in the medical literature, discussed as an educational model, and used generally in the furtherance of medical science. Information from this study may be used as part of a scientific publication in medical or

 _____ Witness' Initials _____ Patient's Initials

professional journals, but you will in no way be personally identified. Complete confidentiality cannot be promised to active-duty military personnel because information bearing on your health may be required to be reported to appropriate medical or command authorities.

Your medical records relating to this study may be reviewed by the U.S. Food and Drug Administration, other government agencies, the Institutional Review Board at Tripler Army Medical Center, The University of Texas Health Science Center at Houston, and U.S. Army Graduate Program in Anesthesia Nursing and results of the study will be reported to them. The recipients will treat this information confidentially. In the event that this study is published, your identity will not be disclosed.

PRECAUTIONS TO BE OBSERVED BY SUBJECT BEFORE AND FOLLOWING THE STUDY: This study may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable. During the course of this study, absence of pregnancy is required. The medications involved in this study may be a significant risk to the fetus if the patient (female) is pregnant. In addition, you should not nurse a baby while on this study.

CIRCUMSTANCES UNDER WHICH YOUR PARTICIPATION MAY BE TERMINATED WITHOUT YOUR CONSENT: (a) Health conditions or other conditions that might occur which may be dangerous or detrimental to you or your health; (b) if military contingency requires it; (c) if you become ineligible for military care as authorized by Army regulation; (d) if the safety monitor determines that continued treatment under this study may be harmful to you.

ADDITIONAL COSTS TO SUBJECT THAT MAY RESULT FROM PARTICIPATION IN STUDY: In accordance with AR 40-38, paragraph 3-3(j)(2), daily charges for inpatient care will be waived while the volunteer is in the hospital if the volunteer would not normally enter the hospital for treatment but is requested to do so as part of a research study or as a result of adverse reaction to the drug(s) or procedure(s) used in this study. This also applies to the volunteer's extension of time in a hospital for a research study when the volunteer is already in the hospital.

SIGNIFICANT NEW FINDINGS: Any significant new findings developed during the course of this study, which could affect your willingness to continue participation, will be made available to you. The results of the research will be made available to you if you so desire. Complete results may not be known for several years.

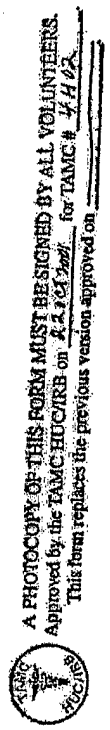
APPROXIMATE NUMBER OF SUBJECTS INVOLVED IN THE STUDY: 60 patients at TAMC

Witness' Initials _____ Patient's Initials _____

Volunteer Agreement Affidavit

DOMICILIARY CARE STATEMENT: The extent of medical care provided, should it become necessary, is limited and will be within the scope authorized for Department of Defense (DOD) health care beneficiaries. Necessary medical care does not include domiciliary (home or nursing home) care.

FOR FURTHER INFORMATION: Please contact the principal investigator, CPT Elizabeth Pulatie at (808) 433-2132.



Witness' Initials _____ Patient's Initials _____

Volunteer Agreement Affidavit

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING. A COPY OF THE VOLUNTEER AGREEMENT AFFIDAVIT WILL BE PROVIDED TO YOU.

******

I have read the above explanation and agree to participate in the investigational study described.

If you are a female, you must read the following two (2) sections:

During the course of this study, absence of pregnancy is required. The medication involved in this study may be a significant risk to me or the fetus if I am pregnant.

I do not believe that I am pregnant and I agree to prevent pregnancy during the course of this study. If there is a possibility of pregnancy (a late period and/or sexual activity without birth control), I agree to request testing and evaluation to diagnose pregnancy before participating in this study. This request, testing and evaluation will be handled with guarantees of privacy and confidentiality, and the results will be made available only to me and/or my doctor. If pregnant, I agree to withdraw from this study and seek medical attention.

_____ _____

Typed Name & Signature of Volunteer Date

_____ _____

Typed Name & Signature of Witness Date

A PHOTOCOPY OF THIS FORM MUST BE SIGNED BY ALL VOLUNTEERS.
Approved by the TAMC HUC/IRB on 22 Oct 2001 for TAMC # 4412
This form replaces the previous version approved on _____

_____ _____

Witness' Initials Patient's Initials

APPENDIX D

Institutional Review Board Approval Form

MCHK-CI DEC 17 2001

MEMORANDUM FOR CPT Elizabeth K. Pulatie, AN, Directorate of Health Education & Training (ATTN: MCHK-HE), Tripler AMC, HI

SUBJECT: Approval to Initiate More Than Minimal Risk Study

1. Your clinical investigation protocol entitled "TAMC 4H02: A Comparison of Preemptive Administration of Ibuprofen, Rofecoxib, and Placebo in Attenuation of Postoperative Pain Following Gynecological Surgery" was reviewed and approved as More Than Minimal Risk by the Human Use Committee (HUC) at Tripler Army Medical Center (TAMC) on 22 October 2001. The protocol may now be initiated.

2. The protocol is approved for a period of **one year** and must be re-approved for continuation no later than 21 October 2002. You will be notified to submit a progress report for your study using the Detailed Summary Sheet prior to continuing review.

3. Your study presents more than minimal risk to participants. LTC Kevin J. Mork, MC has been assigned as the medical monitor for your study. The medical monitor is responsible for serving as an advocate for the medical safety of research participants in your study. You should discuss your protocol with the medical monitor so that (s)he will be familiar with the protocol's procedures, risks, and inclusion/exclusion criteria. It is your responsibility to immediately notify the medical monitor of any serious or unexpected adverse events that occur during the conduct of your study.

4. In accordance with AR 40-38, the principal investigator must promptly notify the approving authority through the medical monitor and the HUC of any serious or unexpected adverse reactions caused by the clinical investigation. AR 40-7 and 21 CFR 312.32 define a serious adverse reaction as one that results in: (a) death, (b) persistent or significant disability or incapacity, (c) life-threatening situation, (d) inpatient or prolonged hospitalization, or (e) congenital anomaly/birth defect in an offspring, or (f) an important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

5. The HUC prior to implementation must approve changes to either the protocol or the consent form. It is your responsibility to maintain an accurate and accessible file on all consent forms of human subjects participating in the research. Your study and its documentation, including list of volunteers and the executed informed consent statements, are subject to inspection at any time by your chain of command and by such inspectors of official audit agencies. You must maintain your records to facilitate such inspections. Upon completion of the study, you should report this to the Department of Clinical Investigation.

MCHK-CI
SUBJECT: Approval to Initiate More Than Minimal Risk Study

6. Please note that this is NOT an approval to receive extramural resources nor an indication of guaranteed funding from the Department of Clinical Investigation. You must coordinate extramural resource approvals with the Department of Clinical Investigation, Bldg. 40, 433-6709. If any extramural resources are received without DA or MEDCOM approval, the individual who receives them may be found in ethics violation and prosecuted for criminal misconduct.

7. All manuscripts, abstracts, or publicly-released information related to research conducted at or sponsored by TAMC must be submitted to the TAMC Technical Management Board as stated in TAMC Pamphlet 40-31 prior to submission for public release or publication. This includes academic lectures given outside TAMC, letters to the editor and press releases.

8. Your research study has been determined to be of potential importance to the academic and professional program of Tripler AMC. You are to give all possible priority to its completion. Should any problem arise that jeopardizes the success of your research, please notify the undersigned at 433-7171.

Catherine M. Schempp
CATHERINE M. SCHEMPP
COL, AN
Chief, Department of Clinical Investigation
Deputy Chair, Human Use Committee

APPENDIX E

Time Line

Chapters I, II, and III were completed by December 2001. The proposal was presented to the review boards in December of 2001. Trial data collection, consisting of a pilot study with the first 10 patients, began in February 2002. Full data collection was begun in February 2002 and completed by August 2002. Chapters IV and V were completed by September 2002. Final submission of the research to the University of Texas Health Science Center at Houston was October 2002.

APPENDIX F

Budget

1. The Tripler Army Medical Center pharmacy provided ibuprofen at a cost of $0.03 per dose, rofecoxib at a cost of $2.13 per dose, and placebo elixir at a cost of $0.03 per dose.

2. Budget:

I.	Presentation at scientific meeting		
	a. Registration	$425.00	
	b. Airfare	$800.00	
	c. Meals and Incidental	$315.00	
	d. Hotel	$700.00	
II.	Pharmacy	$422.50	
III.	Poster Supplies	$150.00	
IV.	Thesis Costs	$300.00	
V.	Total		$3,112.50

REFERENCES

Agency for Health Care Policy and Research (1992). Acute pain management: operative or medical procedures and trauma [On-line]. Available http://hstat.nlm.nig.gov/tempfiles/is/tempBrPg50320.html

Aida, S., Baba, H., Yamakura, T., Taga, K., Fukuda, S., & Shimoji, K. (1999). The effectiveness of preemptive analgesia varies according to the type of surgery: a randomized, double-blind study. Anesthesia and Analgesia, 89(3), 711-720.

Arnstein, P. M. (1997). The neuroplastic phenomenon: a physiologic link between chronic pain and learning. Journal of Neuroscience Nursing, 29(3), 179-187.

Bensen, W., Fiechtner, J., McMillen, J., Zhao, W., Yu, S., Woods, E., Hubbard, R., Isakson, P., Verburg, K., & Geis, S. (1999). Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. Mayo Clinical Procedures, 74, 1095-1105.

Bjarnason, I., Macpherson, A., Rotman, H., Schupp, J., & Hayllar, J. (1997). A randomized, double-blind, crossover comparative endoscopy study on the gastroduodenal tolerability of a highly specific cyclooxygenase-2 inhibitor, flosulide, and naproxen. Scandinavian Journal of Gastroenterology, 32, 126-130.

Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M., Hawkey, C., Hochberg, M., Kvien, T., Schnitzer, T., & Weaver, A. (2000). Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. The New England Journal of Medicine, 343(21), 1520-1528.

Bonica, J. (1979). Pain terms: a list with definitions and notes on usage. Pain, 6, 249-252.

Bonnel, R., Maria L., Karwoski, C., & Beitz, J. (2002). Aseptic meningitis associated with rofecoxib. Archives of Internal Medicine, 162(6), 713-715.

Burns, N., & Grove, S. (1993). Measurement strategies in nursing. In The practice of nursing research (2nd ed., pp. 355-400). Philadelphia: W.B. Saunders Company.

Campbell, W., & Halushka, P. (1996). Lipid-derived autacoids, eicosanoids and platelet-activating factor. In M. Wonsiewicz, McCurdy, P. (Eds.), Goodman & Gilman's the pharmacological basis of therapeutics (9th ed., pp. 601-616). New York: McGraw Hill.

Camu, F., Beecher,T., Recker, D., & Verburg, K. (2002). The cyclooxygenase (cox) 2 specific inhibitor, valdecoxib is opioid-sparing and provides effective analgesia in primary hip arthroplasty patients. Paper presented at the American Association of Nurse Anesthetist Annual Conference, Orlando, FL.

Carter, J., Ryoo, J., & Katz, A. (1994). Laparoscopic-assisted vaginal hysterectomy: a case control comparative study with total abdominal hysterectomy. The Journal of the American Association of Gynecologic Laparoscopists, 1(2), 116-121.

Cataldo, P., Senagore, A., & Kilbride, M. (1993). Ketorolac and patient controlled analgesia in the treatment of postoperative pain. Surgery, Gynecology & Obstetrics, 176(5) 438-438.

Clemett, D., & Goa, K. (2000). Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. Drugs, 59(4), 957-960.

Clive, D., & Stoff, J. (1984). Renal syndromes associated with nonsteroidal antiinflammatory drugs. New England Journal of Medicine, 310(9), 563-572.

Cousins, M., & Power, I. (1999). Textbook of pain (4th ed.). New York: Churchill Livingstone.

Dahl, V., Raeder, J., Drosdal, S., Wathne, O., & Brynildsrud, J. (1995). Prophylactic oral ibuprofen or ibuprofen-codeine versus placebo for postoperative pain after primary hip arthroplasty. Acta Anaesthesiologica Scandinavica, 39, 323-326.

Dalton, J., Carlson, J., Lindley, C., Blau, W., Youngblood, R., & Greer, S. (2000). Clinical economics: calculating the cost of acute postoperative pain medication. Journal of Pain and Symptom Management, 19(4), 295-305.

Daniels, S., Paul J., Hubbard, R, Recker, D., & Verburg, K. (2002). Preoperative administration of valdecoxib, a potent cox2 specific inhibitor, provides effective postoperative analgesia after foot surgery. Paper presented at the American Association of Nurse Anesthetists Annual Conference, Orlando, FL.

Day, R., Morrison, B., Luza, A., Castaneda, O., Strusberg, A., Nahir, M., Helgetveit, K., Kress, B., Daniels, B., Bolognese, J., Krupa, D., Seidenberg, B., & Ehrich, E. (2000). A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. Archives of Internal Medicine, 160, 1781-1787.

Diemunsch, P., Diemunsch, A., & Treisser, A. (1997). Post cesarean analgesia with ketorolac tromethamine and uterine atonia. European Journal of Obstetrics, Gynecology, and Reproductive Biology, 72(2), 205-206.

Dionne, R., Campbell, R., Cooper, S., Hall, D., & Buckingham, B. (1983). Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. The Journal of Clinical Pharmacology, 23, 37-43.

Dorland, W. (2000). Dorland's illustrated medical dictionary. Philadelphia: W.B. Saunders Company.

Downie, W., Leatham, P., Rhind, V., & Wright, V. (1978). Studies with pain rating scales. Annal of Rheumatic Diseases, 37(4), 378-381.

Falcone, T., Fidela, P., & Mascha, E. (1999). Prospective randomized clinical trial of laparoscopically assited vaginal hysterectomy versus total abdominal hysterectomy. American Journal of Obstetrics and Gynecology, 180(4), 955-961.

Fasthealth Corporation. (2000). Fasthealth [On-line]. Available http://www.fasthealth.com/dictionary/k/ketobemidone.php.

Feldman, M., . McMahon, Alexander. (2000). Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity. Annals of Internal Medicine, 132(2), 134-143.

Ferrante, F. & VadeBoncouer, T. (1993). Opioids. In F. Ferrante, T. VadeBoncouer (Ed.), Postoperative pain management (pp. 145-210). New York: Churchill Livingstone.

Ferraz, M., Quaresma, M., Aquino, L., Atra, E., Tugwell, P., & Goldsmith, C. (1990). Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. The Journal of Rheumatology, 17(8) 1022-1024.

Flaherty, S. (1996). Pain measurement tools for clinical practice and research. Journal of the American Association of Nurse Anesthetists, 64(2), 133-140.

Frandsen, J. L. (1997). Pain Management. In J. Nagelhout, & K. Zaglaniczny (Ed.), Nurse anesthesia (1st ed., pp. 1233-1246). Philadelphia: W.B. Saunders Company.

Garrett, N. (2000). Metabotropic glutamate receptor 1A: Review. Biological Research For Nursing, 1(4), 310-320.

Gibbons, M. & Harm, P. (2000). A comparison of postoperative pain with preemptive administration of intravenous ketorolac versus oral ibuprofen in patients undergoing interval laparoscopic bilateral tubal sterilization. Unpublished master's thesis, University of Texas, at Houston Health Sciences Center.

Green, C., Pandit, S., Levy, L., Kothary, S., Tait, A., & Schork, M. (1996). Intraoperative ketorolac has an opioid-sparing effect in women after diagnostic laparoscopy but not after laparoscopic tubal ligation. Anesthesia and Analgesia, 82, 732-737.

Hirata, T., Ukawa, H., Kitamura, M., & Takcuchi, K. (1997). Effects of selective cyclooxygenase inhibitors on alkaline secretory and mucosal ulcerogenic responses in rat duodenum. Life Sciences, 61(16), 1603-1611.

Huang, J., Taguchi, A., Hsu, H., Andriole, G., & Kurz A. (2001). Preoperative oral rofecoxib does not decrease postoperative pain or morphine consumption in patients after radical prostatecomy: a prospective, randomized, double-blinded, placebo-controlled trial. Journal of Clinical Anesthesia, 13(2), 94-97.

Huskisson, E. (1974). Measurement of pain. Lancet, 1127-1131.

Insel, P. (1996). Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In J. Hardman & L. Limbird (Eds.), Goodman & Gilman's the pharmacological basis of therapeutics (9th ed., pp. 617-657). New York: McGraw Hill.

Jensen, M., Karoly, P., & Braver, S. (1986). The measurement of clinical pain intensity: a comparison of six methods. Pain, 27, 117-126.

Law, S., Southard, K., Law, A., Logan, H., & Jakobsen J. (2000). An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. American Journal of Orthodontics and Dentofacial Orthopedics, 118(6), 629-636.

Lehninger, A., Nelson, D., & Cox, M. (1993). Principles of biochemistry with an extended discussion of oxygen-binding proteins. (2nd ed.). New York: Worth Publishers.

Li, Z., Su, X., & Chapleau, M. (1995). Role of cyclooxygenase metabolites in mediating platelet-induced baroreceptor dysfunction. American Journal of Physiology, 269, 599-608.

Malmstrom, K., Daniels, S., Kotey, P., Seidenberg, B., & Desjardins, P. (1999). Comparison of rofecoxib and celecoxib, two cyclooxygenase-2 inhibitors, in postoperative dental pain: a randomized, placebo- and active-comparator-controlled clinical trial. Clinical Therapeutics, 21(10), 1653-1663.

Margolis, T., Heinrichs, W., & Ratner, E. (1999). Gynecology/infertility surgery. In R. Jaffe, & Samuels, S. (Ed.), Anesthesiologist's manual of surgical procedures (2nd ed., pp. 573-598). Philadelphia: Lippincott Williams & Wilkins.

McCaffery, M., & Pasero, C. (1999). Pain: clinical manual (2nd ed.). St. Louis: Mosby, Inc.

McHugh, J. & McHugh, W. (2000). Pain: neuroanatomy, chemical mediators, and clinical implications. AACN Clinical Issues, 11(2), 168-178.

Mukherjee, D., Nissen, S., & Topol, E. (2001). Risk of cardiovascular events associated with selective COX-2 inhibitors. Journal of the American Medical Association, 286(8), 954-959.

Noble, S., King, D., & Olutade, J. (2000). Cyclooxygenase-2 enzyme inhibitors: place in therapy. American Family Physician, 61, 3669-3676.

Owen, H., Galvin, R., & Shaw, N. (1986). Ibuprofen in the management of postoperative pain. British Journal of Anaesthesia, 58, 1371-1375.

Paice, J., & Cohen, F. (1997). Validity of a verbally administered numeric rating scale to measure cancer pain intensity. Cancer Nursing, 20(2), 88-93.

Parker, R., Holtmann, B., Smith, I., & White, P. (1994). Use of ketorolac after lower abdominal surgery effect on analgesic requirement and surgical outcome. Anesthesiology, 80(1), 6-12.

Pasqualucci, A., De Angelis, V., Contardo, R., Colo, F., Terrosu, G., Donini, A., Pasetto, A., & Bresadola, F. (1996). Preemptive analgesia: intraperitoneal local anesthetic in laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. American Society of Anesthesiologists, Inc., 85(1), 11-20.

Pitcher, B. M. (2001). The effect of pre-emptive administration of dextromethorphan on postoperative pain in patients undergoing interval laparoscopic tubal sterilization. Unpublished master's thesis, University of Texas, at Houston Health Sciences University.

Polit, D., & Hungler, B. (1999). Nursing research: principles and methods (6th ed.). Philadelphia: Lippincott Williams & Wilkins.

Reuben, S., & Connelly, N. (2000). Postoperative analgesic effects of celecoxib or refecoxib after spinal fusion surgery. Anesthesia and Analgesia, 91(5), 1221-1225.

Reynolds, L., Recker, D., Hubbard, R., North, J., & Verberg, K. (2002). Valdecoxib, a potent COX-2 specific inhibitor, is an effective opioid-sparing analgesic in patients undergoing orthopedic surgery. Paper presented at the American Association of Nurse Anesthetists Annual Conference, Orlando, Florida.

Role, P., & Galloway, F. (2000). The preoperative evaluation. In J. Duke (Ed.), Anesthesia secrets (2nd ed.). Philadelphia: Hanley & Belfus.

Saag, K., Van der Heijde, D., Fisher, C., Samara, A., DeTora, L., Bolognese, J., Sperling, R., & Daniels, B., (2000). Rofecoxib, a new cyclooxygenase-2 inhibitor, shows sustained efficacy, comparable with other nonsteroidal anti-inflammatory drugs. Archives of Family Medicine, 9(10), 1124-1134.

Sayed, Y., Gibson, R., Edraki, B., Holbrook, R., & Cohen, S. (1999). Hysterectomy-vaginal or total abdominal. In R. Jaffe, & Samuels, S. (Ed.), Anesthesiologist's manual of surgical procedures (pp. 588-592). Philadelphia: Lippincott Williams & Wilkins.

Schoneboom, B. (1992). Ketorolac tromethamine: a nonsteroidal anti-inflammatory analgesic used as an adjunct for general anesthesia. AANA Journal, 60(3), 304-307.

Sennott-Miller, L., Murdaugh, C., & Hinshaw, A. (1988). Magnitude estimation: issues and practical applications. Western Journal of Nursing Research, 10(4), 415-424.

Silverstein, F., Faich, G., Goldstein, J., Jay, L., Simon, L., Pincus, T., Whelton, A., Makuch, R., Eisen, G., Agrawal, N., Stenson, W., Burr, A., Zhao, W., Kent, J., Lefkowith, J., Verburg, K., & Geis, G. (2000). Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the class study: a randomized controlled trial. The Journal of the American Medical Association, 284(10), 1247-1255.

Thompson, J., Sharpe, P., Kiani, S., & Owen-Smith, O. (2000). Effect of meloxicam on postoperative pain after abdominal hysterectomy. British Journal of Anaesthesia, 84(2), 151-154.

Woolf, C., & Salter, M. (2000). Neuronal plasticity: increasing the gain in pain. American Association for the Advancement of Science, 288(5472), 1765-1768.

Woolf, C., & Mannion, R. (1999). Neuropathic pain: aetiology, symptoms, mechanisms, and management. The Lancet, 353(9168), 1959-1964.

VITA

Elizabeth Katherine Mary Pulatie was born in Roseburg, Oregon on December 16th, 1968, to Richard and Carrolene Eddy. She graduated from Sequim High School, in Sequim, Washington in 1987. Elizabeth attended Peninsula Community College in Port Angeles, Washington from 1987-1988 and from 1991to1992. After completion of pre-nursing classes she attended Oregon Health Sciences University at the Oregon Institute of Technology Campus in Klamath Falls Oregon from 1992 to 1995. In 1995, she graduated with a BSN. Her senior year she completed an ICU preceptorship and upon graduation she attended and completed an ER preceptorship. She was employed as an ICU/CCU nurse in Klamath Falls, Oregon from 1995 to 1997. From 1997 to 1998, she worked at St. Francis Medical Center in Tulsa, Oklahoma in the trauma center. From 1998 to 2000, she worked for Preferred staffing travel agency as an ICU nurse. From 1998 to 1999, she taught both clinical and theory for an LVN program through Summit Career College. She is currently attending phase II of the U.S. Army Graduate School of Anesthesia Nursing at TAMC. Elizabeth is married and has two children.

VITA

Tim Adams was born in Independence, Missouri on March 19, 1971 to Frederick and Barbara Adams. He graduated from Fort Osage High School in Independence in 1989. Tim attended the University of Missouri-Kansas City from 1989 to 1993 and earned a Bachelor of Arts degree in Biology. He then attended Bethany Medical Center School of Respiratory Therapy and graduated in August of 1994. Tim worked as a credentialed Respiratory Therapist from 1994 until 1996. In January of 1995 he began an accelerated nursing program at Rockhurst – Research College of Nursing in Kansas City, Missouri. He graduated with a BSN in December 1995. He began his active duty military service with the Army in March 1996. He worked as a nurse at Tripler Army Medical Center in Honolulu, Hawaii beginning in June 1996. Tim attended the Critical Care Nursing Course, at Madigan Army Medical Center in Tacoma Washington in November 1997 and returned to Tripler and worked as an intensive care nurse until March 2000. He is now attending phase II of the U.S. Army Graduate School of Anesthesia Nursing at TAMC. Tim is married and has two children.

VITA

Richard Westen Breeding was born in Louisville, KY on August 2, 1973 to C.R. and Joyce Breeding. He graduated from Jeffersonville High School in Indiana in 1992. Richard attended the University of Mobile in Alabama where he earned a Bachelor of Science degree in Nursing. After graduating in 1997 he received a commission in the Army Reserves. Richard worked as a staff nurse at Mobile Infirmary Medical center in the Surgical Intensive Care Unit and the Emergency Room. He later accepted a position in Open-heart Recovery at Jewish Hospital in Louisville, KY. Richard began his active duty military service with the Army in March 2000 and attended Officer Basic Course. He is now attending phase II of the U.S. Army Graduate School of Anesthesia Nursing at TAMC. Richard is married.

VITA

Timothy James Bryant was born in Crestline, Ohio on November 5, 1967. He is the son of James and Jackie Bryant. He graduated from Galion Senior High School in 1986. Timothy earned his Bachelor of Science in Nursing from the Ohio State University in 1996. He began his active duty military service with the Army in October 1996. Timothy worked as a medical-surgical and Post Anesthesia Care Unit nurse at Lyster Army Community Hospital at Fort Rucker, Alabama from January 1997 until May 2000. He is now attending phase II of the US Army Graduate Program in Anesthesia Nursing at TAMC. Timothy is married and has two children.

VITA

Jason Noble Ernest was born in Buffalo, New York on August 31, 1971. He is the son of John and Jeri Ernest. He graduated from Newfane Senior High School in 1990. Jason earned his Bachelor of Science in Nursing from the State University of New York at Buffalo in May of 1996, where he graduated Cum Laude. He began his active duty military service with the Army in October 1996. Jason worked as a medical-surgical nurse at Evan's U.S. Army Community Hospital from January 1997 – December 1997. His services were then requested to work on a twenty-four hour observation and step-down unit. Jason worked as the head nurse on the step-down unit from August 1999 – June 2000. He is now attending phase II of the U.S. Army Graduate Program in Anesthesia Nursing at TAMC. Jason is married and has one child.

VITA

Steven Alan Kindle was born in Huron, South Dakota on June 3, 1965. He is the son of Sylvia Isabelle Bies and James Edward Bies. After completing high school, he entered Northern State College in Aberdeen, South Dakota where he received the degree of Bachelor of Science in Business Administration, and also completed a three-year Reserve Officer Training Corps commissioning program. Steven received a regular Army commission in the Quartermaster Corps in May of 1987 and served three years on active duty. After leaving the Army in 1990, he worked in public accounting. In 1995 Steven completed an Associate Degree in nursing program at Tacoma Community College in Tacoma, Washington. Upon graduation he worked in the Special Care Unit at Saint Francis Hospital in Federal Way, Washington. While at Saint Francis Hospital, Steven served in the United States Army Reserve and also completed his Bachelor of Science Degree in Nursing at the University of Washington in Tacoma, Washington. In March 2000, he reentered the Army and attended the Army Medical Department Officer Basic Course, and then began the U.S. Army Graduate Program in Anesthesia Nursing, where he is currently enrolled. Steven is married and has two children.

VITA

Hector Muniz was born in El Paso, Texas on October 14th, 1968, to Hector and Elena. He graduated from Bel Air High School, in El Paso, Texas in 1987. Hector served three years in the Army after high school. He then attended the University of Texas at El Paso from 1991 to 1995 where he graduated with a BSN. After graduation, he was commissioned in the Army and worked as a staff nurse on a telemetry floor at William Beaumont Army Medical Center (WBAMC) in El Paso, Texas from 1996 to 1998. He then attended the operating room course at WBAMC and subsequently was reassigned to Womack Army Medical Center in Fort Bragg, North Carolina from 1998 to 2001. He concurrently was assigned as chief OR nurse on a 20-man forward surgical team. He is currently attending phase II of the U.S. Army Graduate Program in Anesthesia Nursing at TAMC. Hector is married and has four children.