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13. ABSTRACT *(Maximum 200 words)*

A major goal of anesthesia practitioners is to provide a comfortable and expedient recovery from the effects of surgery and anesthesia. This includes the challenge fostered by managed-care of facilitating earlier discharges while also managing postoperative pain. Moreover, consumer knowledge and techological advances are pressing the health care community to seek higher levels of patient satisfaction and cost containment. Elective surgery patients are acquiring greater expectations regarding the perioperative care they receive, which includes absence of recall, minimal pain or discomfort, and absence of nausea following surgery. Each year over 10 million women in the United States alone elect to have surgical sterilization. This is usuall accomplished laparoscopically despite the problems of post-laparoscopic pain, which can be servre enough to warrant an unplanned admission. Ketorolac and ibuprofen have both been studied in this patient population when given preemptively with mixed results; presently there is no conclusive evidence as to which drug is more effective. This prospective, randomized, double-blind clinic trial compared the effects over time when these patients received ketorolac or ibuprofen preemptively. The sam was comprised of 44 subjects undergoing laparoscopic tubal ligation under general endotracheal anesthesia at a regional military medical center for the Pacific Rim. The patients were either ASA category I or II and at least 18 years of age assigned to one of two treatment groups. Group I received 800 mg ibuprofen orally and a 1 ml saline placebo intravenously; conversely, Group II received an oral placebo and ketorolac 30 mg intravenously. Postoperative pain was assessed using an 11 point Numeric Rating Scale (NRS) at seven time intervals.

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A COMPARISON OF POSTOPERATIVE PAIN WITH PREEMPTIVE ADMINISTRATION OF INTRAVENOUS KETOROLAC VERSUS ORAL IBUPROFEN IN PATIENTS UNDERGOING INTERVAL LAPAROSCOPIC BILATERAL TUBAL STERILIZATION

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A Thesis

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ABSTRACT:

A major goal of anesthesia practitioners is to provide a comfortable and expedient recovery from the effects of surgery and anesthesia. This includes the challenge fostered by managed-care of facilitating earlier discharges while also managing postoperative pain. Moreover, consumer knowledge and technological advances are pressing the health care community to seek higher levels of patient satisfaction and cost containment. Elective surgery patients are acquiring greater expectations regarding the perioperative care they receive, which includes absence of recall, minimal pain or discomfort, and absence of nausea following surgery.

Each year over 10 million women in the United States alone elect to have surgical sterilization. This is usually accomplished laparoscopically despite the problems of post-laparoscopic pain, which can be severe enough to warrant an unplanned admission. Anesthesia researchers have sought pharmacologic methods in order to address this challenge, with a contemporary approach being preemptive analgesia.

Non-steroidal anti-inflammatory drugs have been shown to inhibit the release of chemical mediators of pain and inflammation following tissue trauma. This results in the reduction of untoward physiologic and psychological effects, improved patient outcomes, and diminishes the economic effects secondary to unplanned hospital admissions. Ketorolac and ibuprofen have both been studied in this patient population when given preemptively with mixed results; presently there is no conclusive evidence as to which drug is more effective. This prospective, randomized, double-blind clinical trial

compared the effects over time when these patients received ketorolac or ibuprofen preemptively.

The sample was comprised of 44 subjects undergoing laparoscopic tubal ligation under general endotracheal anesthesia at a regional military medical center for the Pacific Rim. The patients were either ASA category I or II and at least 18 years of age assigned to one of two treatment groups.

Group I received 800 mg ibuprofen orally and a 1 ml saline placebo intravenously; conversely, Group II received an oral placebo and ketorolac 30 mg intravenously. Postoperative pain was assessed using an 11 point Numeric Rating Scale (NRS) at seven time intervals. Additionally, a follow-up questionnaire and 24-hour postoperative phone call were used to collect data on the patients' satisfaction of being in the study.

The Student's *t* test was used to determine homogeneity between the two groups. NRS scores were analyzed 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 surgery until bedtime. The bimodal data also had predictive value. In addition, Caucasian patients had significantly more nausea at home ($p<0.01$) than African-American or Hawaiian/Pacific Islander patients.

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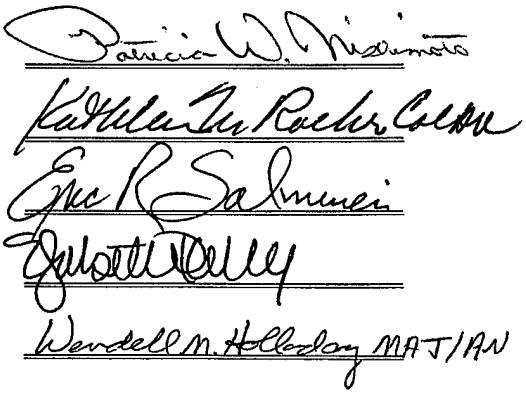

THE UNIVERSITY OF TEXAS
HOUSTON
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The Committee for the
Protection of Human Subjects

NOTICE OF APPROVAL TO BEGIN RESEARCH

October 15, 1999

HSC-SN-99-045 - "A Comparison of Postoperative Pain with Preemptive Administration of Intravenous Ketorolac vs. Oral Ibuprofen in Patients Undergoing Interval Laparoscopic Tubal Sterilization"
PI: Patricia S. Harm, CPT, BSN, MSN Student; et al

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: October 15, 1999 **EXPIRATION DATE**: September 30, 2000

CHAIRPERSON: Anne Dougherty, MD

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

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CHAPTER I

Introduction

A major goal of anesthesia practitioners is to provide a comfortable and expedient recovery from the effects of surgery and anesthesia (Eichorn, 1997). Anesthesia providers have been challenged to facilitate earlier discharges while managing postoperative pain and reducing anesthetic side effects following surgery. Increasing surgical advancements have enabled more procedures to be performed on an outpatient basis (Poole, 1999). Moreover, consumer knowledge and technological advances are pressing the health care community to seek higher levels of patient satisfaction and cost containment. Elective surgery patients are acquiring greater expectations regarding the perioperative care they receive which include absence of recall, minimal pain or discomfort, and absence of nausea following surgery.

Voluntary sterilization is the most commonly used method of fertility control for married couples over 30 years of age, and is the most widely used contraceptive method worldwide protecting over 95 million couples. In addition, over 10 million women in the United States alone have elected to undergo surgical sterilization (Gentile, Kaufman, & Helbig, 1998; Napalitano, Vu, & Rosa, 1996).

Although there are several surgical approaches to female sterilization, the most common procedure is interval laparoscopic bilateral tubal sterilization (ILBTS). This contemporary term, found in the most recent literature, helps to identify tubal sterilization procedures that are not performed at the time of childbirth (Tulondi, 1997). The uterus takes about six weeks after delivery to completely involute, so ILBTS is best performed

at that time (Ryder & Vaughan, 1999). While there are variations of this lower abdominal surgery, the two primary methods are minilaparotomy or laparoscopic approach. The former is normally used in postpartum women; therefore, for the purpose of this study we were interested in the laparoscopic approach as it is most often used in non-pregnant females.

Laparoscopic tubal ligation is routinely performed on an outpatient basis despite the problems of post-laparoscopy pain (Cade & Kakulas, 1995). The degree of pain reported among this post-surgical population can range from menstrual cramping to being severe enough to justify an unplanned hospital admission (Cade & Kakulas, 1995). Researchers who have previously examined pharmacological interventions of providing the most effective pain relief for postoperative ILBTS patients have been unable to conclude which modality is the most efficacious (Guard & Wiltshire, 1996; Hunter & Fogarty, 1996; Kelly, Baker, Robertson, & Noble, 1994; Van EE, Hemrika, De Blok, Van Der Linden, & Lip, 1996). Therefore, the existing variability in post-laparoscopic pain warranted further examination and provided a foundation for our study.

There has been increased interest in preemptive analgesia; that is, to stop or reduce pain from surgery before it begins (Cabell, 2000; Dahl & Kehlet, 1993; Garrett & McShane, 1999; Goodwin, 1998; Woolf & Chong, 1993). In the past, postoperative pain often was treated by the administration of an opioid narcotic (with morphine sulfate considered the gold standard). However, even with careful titration of opioids there can be untoward effects like respiratory depression, somnolence, and postoperative nausea and vomiting. These events may lead to an unplanned hospital admission, which

increases the overall cost of health care delivery and decreases patient satisfaction (Cabell, 2000; Cade, & Kakulas, 1995; White, Joshi, Carpenter, & Fragen, 1997).

Preemptive analgesia follows the premise that it is easier to prevent pain rather than titrate medications to reduce pain once it has already been established (Agency for Health Care Policy and Research, 1997). Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to inhibit the release of chemical mediators of pain and inflammation following tissue trauma. It is theorized that by administering NSAIDs before the ensuing surgical trauma, the chemical mediators of inflammation will be inhibited, which in turn decreases the inflammatory response; therefore, attenuating the resultant pain (Appendix A). Decreased postoperative pain would reduce the untoward physiological and psychological effects, improve patient outcomes, and lessen the economical effects stemming from unplanned hospital admissions.

Although the preemptive administration of ketorolac and ibuprofen have both been studied in this population, the results have been mixed, and to date there is no conclusive evidence as to which drug is more effective. Further investigation is warranted in order to determine if NSAIDs have beneficial effects not only statistically, but clinically as well. Therefore, while NSAIDs have proven benefits when used postoperatively with opioids, their use preemptively remains equivocal.

To address the question of preemptive use of NSAIDs, we designed our study with two treatment groups that were compared over time. Our methodology included random assignment and a double-blind protocol with the two treatment groups; members of each group received one of the NSAIDs and a placebo. Postoperative pain was compared

between the two groups. Also, a follow-up questionnaire and 24-hour postoperative telephone call were used to collect data on the patients' satisfaction of being in the study.

Research Question

Is there a difference in the reported postoperative pain scores, required postoperative opioid usage, or elapsed time until first rescue medication administration following the preemptive administration of either intravenous ketorolac 30 mg or oral ibuprofen 800 mg in patients undergoing interval laparoscopic bilateral tubal sterilization (ILBTS)?

Theoretical Framework

The theoretical framework for this study used a physiological model depicting central and peripheral mechanisms that have been studied in the pain pathway. In addition, a pharmacological model provided a viable approach to preemptively mediate pain that is transmitted by the aforementioned pathways.

The peripheral mechanism for pain modulation begins with nociceptors, which are receptors in the body with the specific role of transmitting noxious stimuli. Noxious sensations are usually communicated along one of two well-defined routes, which are as follows. Sharp, well-localized pain, also referred to as "first pain" is carried by A-delta fibers. Conversely, dull, poorly localized pain, also known as "second pain" is conducted by C fibers. Nociceptors are usually free nerve endings that can sense a specific stimulus. However, polymodal mechanoheat nociceptors can sense temperature extremes, excessive pressure, and respond to alogens (pain-producing substances). Alogens released following surgical trauma or inflammation include prostaglandins, bradykinin, histamine, serotonin, hydrogen and potassium ion, and lactic acid. Prostaglandins induce

a primary hyperalgesic state by increasing the sensitivity of nociceptors in the periphery, therefore increasing the transmission of afferent pain impulses to the central nervous system via the A-delta and C fibers.

Prostaglandins are produced through the following mechanism known as the arachidonic acid cascade. Phospholipase A_2 acts upon membrane phospholipids following tissue damage to form arachidonic acid, which is then converted into PGG_2 and then PGH_2 (endoperoxides) via the cyclooxygenase pathway. The endoperoxides are subsequently transformed into thromboxane A_2 and prostaglandins to include prostacyclin and PGE_2. Prostacyclin increases edema formation from bradykinin, while PGE_2 has a direct effect on free nerve endings. NSAIDs inhibit the cyclooxygenase pathway and thus, the formation of endoperoxides (PGG_2 & PGH_2), the resulting prostaglandins (prostacyclin & PGE_2) and thromboxane (Morgan & Mikhail, 1996).

Central nervous system modulation of pain mainly occurs due to sensitization of second-order neurons. This study was based on knowledge of second-order neurons, which can be nociceptive-specific or wide dynamic range neurons (WDR). WDR neurons maintain discharge frequency and have a prolonged discharge even after afferent C fiber input has ceased by the first order neurons. During wind-up, the excitatory N-methyl-D-aspartate (NMDA) receptors are activated. Activated NMDA receptors increase intracellular calcium concentration in spinal neurons, which activates PLA_2 and subsequent formation of prostaglandins via the arachidonic acid cascade as previously described. Again, NSAIDs inhibit the production of prostaglandins by interfering with

the activity of cyclooxygenase; therefore, appearing to have an important role in the central mediation of pain as well as in the periphery (Morgan & Mikhail, 1996).

The preemptive administration of a pharmacological agent does not necessarily mean treatment before surgical tissue trauma. According to Kissin (1996), emphasis should not be placed on the initiation of treatment, but rather the hyperexcitability and altered sensory processing it is trying to prevent. Since initial tissue injury and subsequent inflammatory responses cause pain, treatment timing should cover the entire duration of noxious stimulation. This is important, as there are two potentially noxious stimuli prior to surgical incision (L. Dahl, personal communication, August 19, 1999). The first noxious stimulus is placement of a peripheral intravenous catheter. In the facility where this study was conducted, the physiologic response was attenuated with the use of buffered 1% lidocaine prior to insertion. The second is direct laryngoscopy and intubation of the trachea. While we acknowledge the sympathetic response is attenuated with intravenous fentanyl given before induction, our design was to have adequate onset time for the NSAIDs used in the study in order to alleviate the inflammatory response. This study examined the effects of two NSAIDs, ketorolac and ibuprofen, on postoperative pain with patients undergoing ILBTS. Our goal was to administer the two drugs a minimum of 30 minutes and 60 minutes, respectively, prior to direct laryngoscopy and intubation of the trachea.

Purpose

The purpose of this study was to examine and compare reported postoperative pain scores, required postoperative opioid usage, and elapsed time until first rescue medication

in patients undergoing ILBTS with the preemptive administration of either ketorolac 30 mg given intravenously or ibuprofen 800 mg given orally.

Definition of Terms

Preemptive analgesia.

Conceptual definition: The implementation of a pharmacologic modality prior to noxious stimuli (to include direct laryngoscopy and tracheal intubation) in order to attenuate post-operative pain. Theoretically, this can be accomplished by interruption of normal pain transmission pathways.

Operational definition: The administration of either intravenous ketorolac 30 mg one half hour before incision, or oral ibuprofen 800 mg one hour prior to incision for the purpose of preventing or decreasing postoperative pain.

Interval Laparoscopic Bilateral Tubal Sterilization (ILBTS).

Conceptual definition: A surgical procedure (in women who are at least six weeks postpartum) involving an opening laparoscopically into the lower abdomen. The fallopian tubes are occluded using either unipolar or bipolar cauterization or mechanical means via application of clips or rings in order to induce occlusion of tissues.

Operational definition: All ILBTS procedures performed on women at Tripler Army Medical Center (TAMC) that (a) meet inclusion criteria, (b) do not fall under exclusion criteria, and (c) consent to participate during the data collection period of 1 November 1999 through 30 June 2000, and (d) receive the standardized anesthetic.

Postoperative pain.

Conceptual definition: A subjective, unpleasant sensory and emotional experience associated with actual or potential tissue damage (The International Association for the Study of Pain, 1999). Includes the perception of an uncomfortable stimulus and the response to the perception.

Operational definition: The complaint of pain (including its severity and location) reported by the patient postoperatively. The subjective complaint of pain will be quantified using a numeric rating scale (NRS). This is an eleven point scale (0-10), with "0" being no pain and "10" being the worst imaginable pain. Pain level will be assessed using the NRS during the perioperative period.

Nonsteroidal anti-inflammatory drugs (NSAIDs).

Conceptual definition: A group of drugs that have analgesic, anti-inflammatory, and antipyretic action. They comprise a variety of drugs (aspirin or aspirin-like) that inhibit the action of cyclooxygenase with a resultant attenuation of the nociceptive response to endogenous mediators of inflammation.

Operational definition: Ketorolac 30 mg given intravenously or ibuprofen 800 mg given orally.

Last Menstrual Period (LMP)

Conceptual Definition: The number of elapsed days since the first day of a woman's last normal menses.

Operational Definition: The number of elapsed days reported by the patient since the first day of her last menstrual cycle. Note: Women who were receiving Depo-Provera® injections and were not menstruating had LMP coded as a missing data point.

Hypothesis

There will be a difference in reported postoperative pain scores, required postoperative opioid usage, or elapsed time until first rescue medication administration in patients undergoing ILBTS who preemptively receive either ketorolac 30 mg intravenously or ibuprofen 800 mg orally.

Significance

Although laparoscopic surgical advances have played a major role in the reduction of postoperative pain and complications in ILBTS patients, the inconsistency in levels of postoperative pain and untoward effects continue to be a challenge to anesthesia providers (Edwards, Barclay, Catling, Martin, & Morgan, 1991; Guard & Wiltshire, 1996; Rasanyagam & Harrison, 1996; White et al., 1997). Mixed results from preceding studies have been unable to unanimously support the preemptive use of NSAIDs with this surgical population (Brodie & Casper, 1985; Cabell, 2000; Cade & Kakulas, 1995; Comfort, Code, Rooney, & Yip, 1992; Edwards et al., 1991; Higgins, Givogre, Marco, Blumenthal, & Furman, 1994; Kelly et al., 1994). Information gleaned from this study pertaining to the preemptive effects of ketorolac and ibuprofen could have clinical implications.

Anesthesia practitioners are compelled to provide an expedient recovery while minimizing the side effects of surgery and anesthesia (Eichorn, 1997). Therefore, current

philosophies are aimed more at the prevention of pain rather than treatment in the postoperative period. Patients whose postoperative pain is absent, or at least at a manageable level will have a more positive experience emotionally and improved physiological outcomes (reduced untoward effects related to nausea, vomiting, incisional pain, & drug-induced somnolence). Unplanned hospital admissions would be reduced, thus generating an economic benefit for the health care delivery system and institution.

Assumptions

1) The patient undergoing ILBTS has postoperative pain.
2) Postoperative ILBTS patients will have similar type pain.
3) Postoperative pain is an undesirable outcome in patients having ILBTS.
4) The pain rating derived from the NRS is an accurate reflection of the level of pain as perceived by the patient (reliability & validity).
5) ASA classifications appropriately identify the patient's health status.
6) Pain is subjective and can be measured most appropriately by the patient.

Limitations

1) This study was conducted in a military, teaching, medical center that may limit generalizability.
2) Results of this study may be generalized only to patients undergoing interval laparoscopic bilateral tubal sterilization receiving general anesthesia.
3) Anesthesia care providers possessing various degrees of preparatory education and clinical experience provided general anesthesia.

Summary

Patients undergoing ILBTS with unmanageable postoperative pain are subject to a host of untoward psychological and physiological side effects. In addition to decreased patient care outcomes and satisfaction, unplanned hospital admissions create an economic burden for a system that is striving to contain the cost of health care. In the double-blind, randomized clinical trial using two groups, we evaluated postoperative pain in patients treated preemptively with either intravenous ketorolac or oral ibuprofen.

The theoretical reasoning to treat preemptively with NSAIDs is that when present in the body, they inhibit the synthesis of prostaglandins both centrally and peripherally. Therefore, the chemical mediation of inflammation is halted and pain is attenuated. It is anticipated that the opioid-sparing effects of the NSAIDs will decrease opioid requirements during the postoperative period; therefore, reducing their inherent side effects such as respiratory depression, nausea and vomiting, constipation, and somnolence. With the successful prevention or reduction of postoperative pain in ambulatory surgical patients, outcomes will be improved, perceptions will be more positive, overall satisfaction will increase, and economic savings will be attained by the health care institution.

CHAPTER II

Review of Related Literature

Interval laparoscopic bilateral tubal sterilization is commonly performed in the outpatient setting (Cade & Kakulas, 1995; Davis & Miller, 1988; Guard & Wiltshire, 1996). The success of ILBTS as an outpatient procedure may be hampered by severe post-operative pain. In fact, the pain after ILBTS is greater than that after diagnostic laparoscopy (Chung, Ritchie, & Su, 1997; Davis & Miller, 1988; Green et al., 1996). The most important factors in the successful management of outpatients undergoing ambulatory surgery is controlling postoperative pain (White et al., 1997). Inadequate pain relief may delay ambulation, prolong discharge, and cause an expensive, unplanned hospital admission.

Challenges exist concerning the treatment of postoperative pain in ILBTS patients. The customary method of treating postoperative pain in this patient population is via opioid analgesia. However, opioids may cause respiratory depression, nausea, vomiting, urinary retention, and sedation (Cabell, 2000; Cade, & Kakulas, 1995; White et al., 1997). These adverse effects may delay or prevent discharge the day of surgery. Researchers have been investigating ways to decrease postoperative pain, and eliminate or decrease the need for opioids. The adjunctive use of NSAIDs has been extensively studied because of their opioid sparing actions. Single, preoperative doses of NSAIDs have generally been proven to be efficacious in decreasing postoperative pain, but they are less efficacious when used as the sole analgesic (Goodwin, 1998; Souter, Fredman, & White, 1994). Combining NSAIDs with a variety of other analgesia

therapies such as local anesthetics, and opioids, as well as employing psychological support is referred to as balanced, or multimodal analgesia (Chung et al., 1997). A review of the literature revealed that taking a multimodal approach may be the most efficacious method in treating postoperative pain following laparoscopic tubal sterilization (Alexander, 1997; Chung et al., 1997; Goldstein et al., 2000; Kelly et al., 1995; Wittels et al., 1998). Nonetheless, controversy exists in the literature concerning the optimal timing, route of administration, and combination of drugs, so further research is needed. The design for this prospective, double-blind, randomized, clinical trial used the multimodal analgesia approach of combining preemptive NSAIDs in conjunction with a local anesthetic and opioids. This study was undertaken to determine which NSAID (ibuprofen or ketorolac), when administered preemptively, is more effective in attenuating pain following ILBTS.

To better understand the background of this study, this chapter first takes a historical approach in looking at the different occlusive methods used in ILBTS, complications associated with the different methods, and types as well as etiology of pain experienced by the tubal ligation patient. The following section examines preemptive analgesia and the two NSAIDs used in this study, ibuprofen and ketorolac.

Interval Laparoscopic Bilateral Tubal Sterilization

Currently, sterilization is the most commonly used method of family planning in the world (Pati, Carignan, & Pollack, 1998). Around 95 million married couples globally depend upon sterilization (either male or female) for contraception. In the United States alone, about 10 million women have used surgical sterilization as their method of

contraception (Gentile et al., 1998; Napalitano et al., 1996). Although there are several surgical approaches to female sterilization, the most common procedure is ILBTS.

Most of the literature on female sterilization was written in the 1970's. Those were the pioneer days of laparoscopy, and tubal occlusion was the only recognized operative technique. By the1990's, very little had been added to what was known about female sterilization, but interest in the subject was renewed in 1997. The findings from the United States Collaborative Review of Sterilization (CREST) study were published at that time.

The CREST study was a large (10,863 female subjects), prospective, multicenter (16 medical centers) study undertaken by the Center for Disease Control (CDC) to examine long-term failure rates, and other issues related to tubal sterilization. After their sterilization procedures, the subjects were followed by annual telephone interviews ranging from eight to fourteen years. The study included data from 10,685 subjects, with only 178 lost to analysis from attrition, hysterectomy, or death. The study used failure rates calculated as cumulative rates over ten years. The ten year cumulative failure rate for all types of occlusion methods was 18.5 per 1000 procedures at a 95% confidence interval (range of 15.1 to 21.8). Unipolar coagulation and postpartum partial salpingectomy had the lowest failure rate of 7.5/1000. Falope bands had the next lowest failure rate of 17.7/1000. The spring-loaded clip and bipolar coagulation had failure rates of 36.5/1000 and 24.8/1000 respectively, making them the methods with highest failure rates (Peterson et al., 1997).

This literature review uses the CREST study because the investigators took a historical approach in presenting the morbidity of tubal sterilization, as well as failure rates. In reviewing the different occlusive techniques, there will be a clearer understanding of the benefits and limitations of each method, as well as the differing amounts of pain experienced. The following is a chronological historical review of the different tubal sterilization techniques on which the CREST study researchers collected data.

In 1962, the modern technique of laparoscopic tubal electrocoagulation was first performed. This electrical procedure was unipolar in nature. Electrical energy in the unipolar technique is concentrated at the site at which the fallopian tube is grasped in the jaws of the forceps. The electrical current travels from that site through the patient's body, and exits through a "ground plate" via a pad placed on the patient's buttocks or thigh. Today, unipolar coagulation has fallen into disfavor because of the risk of thermal injury to intraabdominal organs in addition to the availability of safer methods. However, the Crest study's 10 year cumulative life-table method of specific probabilities of sterilization failure demonstrated that laparoscopic unipolar coagulation is one of the most effective methods of female sterilization (Peterson et al., 1997).

In 1972, Rioux devised the bipolar forceps for tubal electrocoagulation. This method differs from the conventional unipolar system in that the operating forceps carries both the active and the return electrode. The two jaws of the forceps are completely isolated from one another; high-frequency current can be passed through one jaw to the tissue grasped between the jaw, and returned to the generator through the other jaw. The current

passes only through the tissue grasped between the jaws of the forceps, with very minimal spread to the adjacent tissue. This method appeared to be safer than the unipolar system, because the number of electrical burns declined rapidly with its increasing use (Rioux, & Yuzpe, 1997). However, the CREST study investigators found that bipolar coagulation (the most common occlusion method used in the U.S. for interval sterilization) is associated with one of the highest failure rates and the highest ectopic pregnancy rates (Peterson et al., 1997). The CREST investigators found that both types of electrocoagulation techniques cause less pain than mechanical techniques (especially the Falope ring). A reasonable explanation for a decreased amount of pain experienced following electrocoagulation may be that when the tube is occluded a third degree burn is created, thus destroying the nerve endings.

In 1973, Hulka developed a new mechanical method of occlusion using a spring-loaded device known as the Hulka clip. As described by Hulka and Reich (1994), the spring clip is applied after the fallopian tube is stretched, and then is placed on the proximal isthmus 1-2 cm from the uterotubal junction. The clip needs to be applied at a 90-degree angle to the long axis of the fallopian tube. Before the jaws of the clip are closed, the clip is advanced over the tube until the tube reaches the hinge of the clip. When closed, the clip should include a small portion of mesosalpinx (the proximal part of the fallopian tube). According to the CREST study, this technique had the highest failure rate, but it is the method most likely to be successfully reversed by tubal anastomsis.

Another mechanical approach developed in 1975 was Yoon's Falope ring. Rioux and Yuzpe (1997) describe this method as having a loop of tube drawn up within the central

hollow cylinder of the applicator forceps, and a silastic band loaded on the outside of the applicator. The band is forced down over the loop of tube by the action of an outer cylinder. The part of the tube where the ring is applied becomes sclerosed. Sometimes the ring falls off or it may become covered by peritoneum. The CREST study researchers found the tubal ring to be the third most effective occlusive method. The ring method results in the loss of one to two and a half centimeters of functional tube. This occurs because of necrosis of the segment enclosed within the ring. Secondary to necrosis, the Falope ring method is almost impossible to reverse and causes the most postoperative ischemic pain. Previous studies (Chi & Cole, 1979; Dobbs, Kumar, Alexander, & Hull, 1987; Pelland, 1977) lend support to the finding that pain following placement of Falope rings is associated with greater pain than with electrocoagulation or the Hulka clip.

The Filshie clip was developed in 1981 but was not approved by the FDA for use in the U.S. until 1997. Therefore, the Filshie clip was not included in the CREST study. Rioux and Yuzpe (1997) described Canadian practitioners as having a very positive experience with the Filshie clip due to its efficacy, low failure rate, and a high degree of reversibility. The difference between the Hulka clip and the Filshie clip is that the Filshe clip has jaws of titanium lined by a cushion of silicone rubber. The Hulka clip has interlocking teeth made of plastic. Since the silicone rubber on the Filshie clip is soft, adjustment of the application site causes no tubal injury or bleeding. The Hulka clip may cause injury and some bleeding from the tube when repositioned.

The last surgical method to be evaluated by the CREST researchers was the postpartum partial salpingectomy (Pomeroy technique). This technique is done during

cesarean delivery or by minilaparotomy. Ligation and excision of a mid-isthmic loop of the fallopian tube completes sterilization. The CREST study listed this method as being both safe and the most effective sterilization technique. However, this method was related to the most post tubal sterilization regret. The regret was attributed to the women rendering quick decisions about sterilization shortly after delivery. ILBTS was found to have a lower incidence of regret due to the women taking more time to finalize their decision to have tubal sterilization.

The findings of the CREST study added new and surprising information to the field of female sterilization. Initially, the first year after sterilization was thought to be when most failures occurred, however, the CREST data showed that was not true. The researchers of the CREST study found that cumulative failure rates rose steadily through ten years post-sterilization, and that younger women are at greatest risk of failure secondary to their many years of potential fertility. Because the CREST study did not examine exactly how each occlusion method was performed, and the study was conducted at teaching institutions, caution must be exercised in generalizing the findings. The surgeons (often residents) at teaching institutions may have been less experienced in tubal occlusion techniques.

In summary, since 1962 various approaches to tubal ligation have been used. They are unipolar and bipolar electrocoagulation, Hulka clip, Yoon's Falope ring, Filshie clip, and Pomeroy technique. All but the Filshie clips were evaluated over a 14-year period. Each technique has benefits and limitations, and different amounts of postoperative pain. The relative effectiveness, safety, equipment costs, and ease of

application are some of the important variables to consider when selecting a tubal occlusion technique.

The Falope ring is the most common occlusive method performed at TAMC (80%) because it is quick and easy to apply, has one of the lowest failure rates, and thermal burns to adjacent tissues are avoided (E. Salminen, personal communication, August 12, 1999). The disadvantages of using the Falope ring are related to the ischemia and subsequent necrosis that develops following placement. This occlusive technique is almost impossible to reverse due to fallopian tube necrosis. Also, multiple studies have found this technique to be the most painful (due to ischemia to the tubes); therefore, it presents an analgesic challenge.

Pain from Tubal Sterilization

Four types of pain after laparoscopic sterilization have been reported. Subphrenic/ shoulder pain is the first type of pain. This is referred pain, and appears to arise from the persistence of intraperitoneal carbon dioxide. This irritates the diaphragm and phrenic nerve, and may persist until the third to fourth postoperative day (Alexander, 1997; Dobbs et al., 1987; Goldstein et al., 2000; Guard & Wiltshire, 1996). Deep pelvic pain is the second type of pain and is attributable to the use of clips, rings or electrocoagulation to occlude the fallopian tubes. This pain, though severe, rarely persists for more than six hours postoperatively (Alexander, 1997; Chi & Cole, 1979; Davis & Miller, 1988; Dobbs et al., 1987; Goldstein, 2000; Pelland, 1987). Incisional pain is the third type of pain, and is caused by trocar insertion into the abdomen. Studies have not addressed it specifically because it is perceived as being incidental (Cade & Kakulas, 1995;

Rasanayagam & Harrison, 1996; White, 1997) Spasmodic/cramping pain is the fourth type of pain, and like deep pelvic pain is attributable to the use of clips, rings, or electrocoagulation to occlude the fallopian tubes. This pain also has been depicted as being severe, but rarely persists for more than three to four hours (Dobbs et al., 1987: Edwards et al., 1991; Guard & Wiltshire, 1996). Laparoscopic sterilization represents an analgesic challenge due to the different sources of pain.

The subphrenic/shoulder pain is best attenuated by the complete aspiration of carbon dioxide gas before closing the trocar sites (Alexander, 1997; Dobbs et al., 1987; Guard & Wiltshire, 1996). However, the focus of this review is on abdominal pain (deep pelvic and spasmodic/cramping types of pain). Drug modalities for this type of pain vary in regard to the use of opioids, NSAIDs, antispasmodics, and local anesthetics. As previously stated, many anesthesia researchers recommend employing a multimodal analgesia approach in attenuating postoperative laparoscopic sterilization pain (Alexander, 1997; Chung et al., 1997; Goldstein, 2000; Kelly et al., 1995; Wittels et al., 1998).

Studies have shown that the incidence and severity of pain after laparoscopic sterilization is reduced with the use of local anesthetics (Ezeh et al, 1995; Goldstein, 2000; Pelland, 1976; Tool, Kammerer-Doak, Nguyen, Cousin, & Charsley, 1997, & Van EE et al., 1996). Application can be accomplished through the following routes: installation into the peritoneum, drops applied directly onto the fallopian tubes, or by direct injection into the mesosalpinx.

Ezeh et al. (1995) did a randomized, double-blind, placebo-controlled trial to determine the effectiveness of 2% lignocaine gel versus K-Y gel when applied to Filshie clips during tubal sterilization. The study consisted of 80 healthy women undergoing tubal sterilization at a county hospital in the United Kingdom. A 100 mm visual analog scale (VAS) was used to assess pain at 1 hour postoperatively, time of the first analgesia medications postoperatively, and discharge.

One of the findings of this study was that postoperative analgesics were administered more often in the placebo group than in the treatment group. The investigators found that the pain intensity scores assessed at the time of the first postoperative analgesia medication and at discharge were similar in both groups. However, the VAS scores were significantly lower at 1 hour postoperatively for the lignocaine group. The authors acknowledged the need for a long acting and potent anesthetic gel (etidocaine or bupivacaine) to be used instead of a short acting agent, in order to provide longer pain relief. Unfortunately at the time of the study, etidocaine gel was not available in the UK, and bupivacaine gel was only available in combination with other additives.

A weakness of this study is that data analysis did not include the actual time of discharge from the hospital. If the time of discharge was after three to four hours, and the subjects were having spasmodic/cramping type pain (which usually subsides in three to four hours), that may be one of the reasons for no significant difference in pain scores at discharge. Furthermore, if there were any differences in pain scores after discharge, that data was not captured.

Guard and Wiltshire (1996) evaluated the contribution of tubal spasm to pelvic pain following laparoscopic sterilization. This was the only study in the literature that measured the effects of using an antispasmodic agent (glycopyrrolate) to decrease postoperative pain and analgesic requirements following laparoscopic sterilization. This double-blind, randomized, placebo-controlled study was conducted with 60 outpatients presenting for laparoscopic sterilization using Filshie clips. Seven subjects were excluded from the study, leaving 27 in the glycopyrrolate group and 26 in the placebo group. All subjects were premedicated with diclofenac 100 mg rectally (time of administration was not indicated). They were then randomly assigned to receive either glycopyrrolate (0.3mg in 1.5 ml) or saline (1.5 ml).

The results demonstrated a significant reduction ($p< 0.01$) in pain scores postoperatively in the glycopyrrolate group. Also, the researchers found a significant decrease in postoperative morphine administration in the glycopyrrolate group. A weakness in this study is that the first pain score was evaluated just before the patients left the recovery ward. By that time, 22% of the glycopyrrolate group and 67% of the control group had received morphine. There may have been an even greater difference in pain intensity between the groups at the time of admission to recovery room, and in the immediate postoperative period. No discharge follow up was conducted, but the investigators justified this by stating they were targeting spasmodic type of pain, which usually subsides in three to four hours.

Rasanayagam and Harrison (1996) looked at the analgesic effect of the

preoperative oral administration of an opioid (morphine 10 mg) on VAS pain scores after gynecological laparoscopy. The researchers had been using morphine sulfate tablets preoperatively for laparoscopic patients, and clinically had the impression that the patients were more comfortable postoperatively. This study was designed to test their anecdotal perceptions. Two groups of 56 subjects were in this randomized, prospective, double-blind, and placebo-controlled study. One group underwent diagnostic laparoscopy and the other group underwent laparoscopic sterilization. The two groups were divided into 4 subgroups: laparoscopic sterilization morphine group, laparoscopic sterilization placebo group, diagnostic laparoscopy morphine group, and diagnostic laparoscopy placebo group.

The results of the study showed that premedication with morphine 10 mg orally did not significantly decrease pain in any of the subgroups studied. A plausible explanation for no difference between the groups may be that the oral morphine sulfate was administered at the same time as oral naproxen one gram (all groups received the naproxen). The combination may have delayed gut motility, and hence the bioavailability of both drugs. The study did show greater pain scores and increased need for analgesics in the laparoscopic sterilization group as opposed to the diagnostic laparoscopy group. This is consistent with the results of other duplicate studies comparing these two groups.

The next part of this section will examine two studies on the preemptive administration of NSAIDs in the laparoscopic tubal sterilization patient. Additional NSAID studies in this patient population will be covered in subsequent sections.

Brodie and Casper (1985) conducted a double-blind, randomized, placebo-controlled, study examining the efficacy of the preoperative administration of indomethacin in reducing the incidence of postoperative pain in patients undergoing Falope ring tubal occlusion. Sixty-five consecutive patients undergoing elective Falope ring sterilization, over a six month period, were randomly assigned to one of two groups. The study group (19 patients after attrition) received a 100 mg indomethacin rectal suppository immediately after induction. Patients in the control group (33 patients after attrition) received nothing. Postoperatively all the patients received mepreidine 50 mg intramuscularly (up to two doses 30 minutes apart). If the patients were still complaining of pain 30 minutes after the second injection of meperidine, a 100 mg indomethacin rectal suppository was administered.

The researchers found that none of the 19 study patients required a second indomethacin suppository, while eight of the 33 control patients did. The difference between the groups was statistically significant (using chi square for analysis, $p<0.02$). A weakness of this study was that the indomethacin suppositories were administered after induction, so the tubal occlusions were all performed before peak indomethacin concentrations were obtained (mean duration of surgery was 17 minutes versus 30 to 60 minutes for peak therapeutic levels). If the suppositories had been given at least one hour prior to induction, there may have been an even greater reduction in the amount of pain postoperatively.

Comfort et al. (1992) undertook a similar double-blind, randomized, placebo-controlled clinical trial on patients undergoing outpatient laparoscopic tubal ligations.

This study evaluated the effectiveness of naproxen sodium 550 mg oral preemedication in reducing postoperative pain, analgesic requirements and length of stay. Forty-four patients completed the study with 21 patients in the naproxen group and 23 in the control group. The researchers found a statistically significant difference ($p<0.05$) between groups in terms of pain score, postoperative opioid requirements, and length of stay (all lower in the naproxen group). This study had a tighter design compared to Brodie and Casper's (1985) in that the naproxen was given one hour prior to induction. Naproxen has a peak plasma concentration of 20-40 minutes.

Van EE et al. (1996) completed a double-blind, randomized, placebo-controlled study evaluating the effect of the preoperative administration of ketoprofen and mesosalpinx infiltration, either alone or in combination (multimodal), on the postoperative recovery of the laparoscopic sterilization patient. The 60 women in the study were divided into three groups. The first group received oral ketoprofen 100 mg preoperatively, and mesosalpinx was injected intraoperatively with 5 ml saline plus epinephrine 1:200,000. The second group received oral ketoprofen, and mesosalpinx was injected with 5 ml of bupivacaine 0.5% with epinephrine. The last group received a placebo pill and mesosalpinx was injected with 5 ml of bupivacaine 0.5% with epinephrine.

The researchers found that the postoperative pain ratings in the group who received ketoprofen alone were significantly higher ($p<.001$) than the pain ratings in the other two groups. Nausea and vomiting were also the highest, as well as longer discharge times, in this group. Median time to discharge in this group was 385 minutes, with a

range of 260-510 minutes. This was a significant difference ($p< 0.001$) from the other two groups. Combining preoperative ketoprofen and 0.5% bupivacaine mesosalpinx block resulted in the lowest amount of postoperative analgesic administration, the lowest incidence of nausea and vomiting, and the shortest times to discharge (median 190 minutes with a range 80-330 minutes).

The researchers concluded that mesosalpinx infiltration with local anesthetic has a positive effect on the postoperative recovery from laparoscopic sterilization. However, the multimodal analgesic approach of combining local injection with oral ketoprofen resulted in better outcomes. A plausible reason for the improved results with the multimodal approach may be that ketoprofen offered prolonged analgesia after the local anesthetic had dissipated.

In summary, five prospective, double-blind, randomized, placebo-controlled studies of women undergoing laparoscopic tubal sterilization were reviewed in this section. Local anesthetics, antispasmodics, opioids, NSAIDs, and multimodal analgesia were the drug modalities that were evaluated. All the modalities were effective in attenuating postoperative abdominal pain following laparoscopic tubal sterilization.

In order to have a stronger design, the current study incorporated some of the strengths, and avoided the limitations of the studies reviewed above. First, the design was for the NSAIDs to be administered so that theoretically peak concentrations were obtained prior to induction. Second, a standardized anesthetic as well as surgical procedure was incorporated. Third, data collection times were from fifteen minutes after surgery to bedtime, in order to capture most of the changes that occur with pain intensity

following laparoscopic tubal sterilization. Fourth, the design included qualitative analysis of the type and location of pain experienced by the study participants. Last, the multimodal approach of combining the preemptive administration of an NSAID, opioids for induction and as rescue analgesia, and application of a long acting local anesthetic (bupivicaine) to the fallopian tubes was adopted.

Preemptive Analgesia

On a physiological basis, pain itself can be described as the unpleasant sensation that is derived from stimuli to a series of nociceptive receptors throughout the body (Reisine & Pasternak, 1996). Garrett and McShane (1999) described pain as being a complex psychologic as well as physiologic reaction to potential or actual tissue damage. In other words, pain is a dynamic event modified by experience, culture, and emotions. It is not just a physiologic event. Only the physiologic process will be discussed in this review.

The physiologic process starts with acute tissue disruption and/or nerve injury (this happens with laryngoscopy), which eventually leads to stimulation of both the peripheral and central nervous systems (Lubenow, Ivankovich & McCarthy, 1997). Peripheral sensitization is the term given to the following series of events. Tissue trauma activates free pain nerve endings called primary afferent nociceptors. Once activated, nociceptors transmit their signals to the spinal cord by A-delta fibers and C fibers. Stimulation of nociceptors causes the release of potassium ions as well as a variety of chemical mediators (prostaglandins, bradykinin, histamine, serotonin, substance P, and cytokines). These substances sensitize the primary afferent nocieptors in the periphery.

This sensitization effects the primary afferent nociceptors in the following way: (a) decreased threshold for stimulation, (b) activation of nociceptors that were not previously responsive to the stimuli, and (c) increased transmission to the spinal neurons, also called second order neurons (Garrett & Mcshane, 1999; Goodwin, 1998).

Central sensitization is the result of an increase in the excitability of second order neurons, which is triggered by and outlasts primary afferent nociceptive input. Primary afferents synapse with second order neurons in the dorsal horn of the spinal cord, and release excitatory amino acids, substance P, and glutamate. Increased input into the dorsal horn due to peripheral sensitization causes changes in the second order neurons. These changes are: (a) primary hyperalgesia, which is an exaggerated response to noxious stimuli; (b) allodynia, which is a reduction in the intensity of stimuli necessary to initiate pain so that stimuli that would never normally produce pain begin to do so; and (c) secondary hyperalgesia, which is the spread of hypersensitivity to noninjured tissue (Woolf & Chong, 1993).

The combination of peripheral and central sensitization result in a phenomenon called hypersensitivity/hyperalgesia (wind-up). Glutamate and the excitatory amino acids bombard the second order neurons until eventually NMDA glutamate receptors are stimulated. Activation of the NMDA receptors contributes substantially to the persistent nociception and hyperalgesia, even after acute tissue trauma has ended in the periphery. Once this hyperalgesia is propagated, it is very difficult to stop (Garrett & McShane, 1999; Goodwin, 1998; Woolf & Chong, 1993).

One strategy for preventing hypersensitivity postoperatively is to prevent or minimize the activation of second order neurons (which can happen with high level nociception in the periphery), by pharmacologic blockade, before the stimulation occurs (laryngoscopy is considered to be even more stimulating then surgical incision). This theory is known as preemptive analgesia (Woolf & Chong, 1993).

In 1913, George Crile introduced the idea that post-surgical pain could be prevented (preempted) by hindering the flow of painful stimuli to the brain (Penning, 1996). Although Crile advocated this technique many years ago, it fell out of favor until its revival in the early 1980`s. The resurgence of this theory came about with a series of experimental studies conducted by Woolf (1983) and Wall (1988). To date much of the research has been inconclusive as to the effectiveness of varying the timing of preemptive analgesia. However, there does seem to be consensus that Crile's original hypothesis of peripheral desensitization can affect the amount of stimuli sent to the central nervous system.

While Crile originally practiced regional blockade in combination with general anesthesia, it is evident that there are other mechanisms available to block hyperalgesia (Kissin, 1996). Controversy exists in the literature concerning the route of administration, as well as the optimal combination of drugs. Also open to debate, is whether hypersensitivity can best be prevented by blocking peripherally or centrally, before or after surgery, or combinations of the two. An overview of some of the drugs, techniques, and mechanism of action currently used for preemptive analgesia is discussed in the following section.

NMDA Receptor Antagonists

Ketamine has been shown to block (non-competitively) the NMDA receptors by binding to the PCP recognition site in the NMDA receptor channel. Abdel-Ghaffar, Abdulatif, Al-Ghamdi, Mowafi, and Anwar (1998) studied in a prospective, randomized, double-blind, placebo-controlled design, the analgesic effect of epidural ketamine on postoperative pain and epidural PCA consumption after total abdominal hysterectomy. Sixty-one women aged 34-60 years were randomly assigned into three groups. Group One received 30 mg of epidural ketamine prior to induction. Group Two received 30 mg of epidural ketamine 20 minutes after skin incision. Group Three received a placebo. Analgesia was maintained postoperatively by epidural PCA with a mixture of bupivacaine and fentanyl.

The results of the study showed that epidural ketamine prolonged the time to first analgesia request, and reduced postoperative epidural PCA consumption. This effect happened whether ketamine was given before induction or after skin incision. The researchers could not demonstrate any differences in pain scores or PCA analgesic consumption between Group One and Group Two. Power analysis indicated that a larger study (116 subjects in each group) was required to demonstrate a difference in PCA consumption between Groups one and Two.

A possible reason for no difference between Groups One and Two other than the small sample size might be similar to the findings of a 1991 animal experiment. Woolf and Thompson (1991) conducted a study using rats and found that NMDA antagonists not only prevent wind up, but also reduce wind up once it is established. The question is,

can animal research be transferred over to humans? The researchers conducting this study choose the epidural route for the administration of ketamine in order to avoid psychotomimetic side effects (high concentration of ketamine at the spine segments with minimal systemic effects). None of the patients in the study experienced hallucinations.

Dextromethorphan is another noncompetitive antagonist at the NMDA receptor. Henerson, Withington, Wilson, and Morrison (1999) examined the effect of dextromethorphan on postoperative pain by assessing the effect on both analgesic requirements and pain scoring after abdominal hysterectomy. Fifty women aged 30-60 years were recruited for this double-blind, randomized, placebo-controlled clinical trial.

The subjects were randomly assigned to two groups. The first group (Group DM) received oral dextromethorphan 40 mg 90 minutes prior to surgery, 40 mg on the evening after surgery, and then 40 mg three times per day for the next two days. The second group (Group P) was given placebo capsules (lactose) at identical times. Morphine PCA was used for the first 24 hours postoperatively, and replaced with oral analgesia after that.

Analysis was completed on 24 patients in Group DM, and 23 patients in Group P. Median VAS pain scores at rest were lower in Group DM at all time points, reaching statistical difference at 48 hours and 72 hours. Also, the sum of all resting pain scores over the first three days was significantly lower in Group DM. In the first 24 hours, the mean amount of PCA morphine used was greater in Group P, but this did not reach statistical significance. None of the patients in this study experienced psychotomimetic side effects. The results of this study, and the one above, demonstrate that the addition of

an NMDA receptor antagonist to the multimodal analgesia armamentarium holds promise.

NSAIDs

O'Hanlon, Muldoon, Lowry, & McCleane (1996) in a prospective, placebo-controlled study, compared the effects of 20 mg of piroxicam given at different times in the perioperative period on postoperative analgesic requirements. Sixty women presenting for inpatient gynecological laparoscopic surgery were given either 20 mg piroxicam or an oral placebo two hours preoperatively, immediately before induction of anesthesia or one hour postoperatively in a randomized double-blind manner.

The results of the study showed a significant reduction ($p< 0.04$) in total postoperative analgesic requirements for gynecologic laparoscopy patients, as well as a significant delayed onset ($p< 0.05$) of post-surgical pain with the use of piroxicam preoperatively. The patients in Group I who received 20 mg of piroxicam two hours preoperatively requested less analgesia and had a longer time to first analgesic request than patients given piroxicam prior to induction or postoperatively.

The investigators did not study patients undergoing tubal sterilization. Pain following laparoscopic tubal sterilization has been shown to be greater then pain following diagnostic laparoscopy. There are several limitations that impact on the findings of this study. First is the lack of a definition for the types of gynecological procedures that the women underwent. Next is the lack of reported data on the dispersal of the procedures between the groups. There are many different types of laparoscopic gynecological procedures, and the pain experienced postoperatively can vary widely. More studies

involving ibuprofen and ketorolac (the two NSAIDs used in this study) will be reviewed later in this chapter.

Local Anesthetics

Wheatley, Miller, and Jadad (1994) found a reduction in pain after laparoscopic sterilization when 10 ml of 0.5% bupivacaine was dripped on the fallopian tubes prior to occlusion. Sixty women presenting for same day laparoscopic sterilization were in this randomized, double-blind, placebo- controlled trial. Time to first postoperative analgesia, and pain levels (VAS) at 1 hour, and at discharge, and at time of first analgesia were measured. Group S received 10 ml of 0.9% normal saline, and Group B received 10 ml of 0.5% bupivacaine.

The results of this study showed that Group B 's time to first analgesia was significantly longer (p= 0.03), and had lower VAS scores (p=0.04) at the one hour assessment. By the time of discharge, there was no difference between the groups. A weakness of this study is observer bias, which is a threat to external validity. The postoperative pain medication in this study design was administered not only according to the severity of the pain assessed by categorical verbal pain scale, but also if the recovery nurses thought that the patient looked uncomfortable. Another limitation to this study is the lack of data on the type of occlusion technique or techniques applied to the fallopian tubes. As previously stated there is varying amounts of pain between the different occlusive techniques.

Goldstein et al. (2000) tested the hypothesis that postoperative pain at wake-up and during the first 24 hours following laparoscopic gynecologic procedures is prevented

by the instillation of local anesthetics at the end of surgery. One hundred eighty women were randomly assigned to three groups in this prospective, double-blind, placebo-controlled study. Each group received a 20 ml intraperitoneal instillation of either bupivacaine 0.5% (Group B), ropivacaine 0.75% (Group R), or saline (Group S). The standard postoperative analgesia regimen, in the hospital where this study took place, included the administration of acetaminophen, NSAIDs, and morphine. An infusion of propacetamol (2 g) and ketoprofen (100 mg) was started 30 to 60 minutes before completion of surgery, and was repeated every six hours for the first 24 hours postoperatively.

Using a ten point numeric scale (NS), the nurses in the PACU assessed the level of pain every five minutes. Intravenous morphine (2 mg) was administered if the NS score was greater than four, and repeated every five minutes until a score of four or less was obtained. Assessment of pain was continued every four hours for the next 24 hours. Morphine consumption at wakeup and during the first 24 hours was selected as the two efficacy variables to determine if there was difference in postoperative pain.

The researchers found that morphine consumption at wakeup and during the first 24 hours postoperatively was significantly smaller in Groups B and R compared to Group S. Also, morphine consumption was significantly less in Group R compared to Group B. The researchers concluded that local anesthetics should be instilled, at the end of surgery, in all patients undergoing laparoscopic procedures. They stated that the best choice is ropivacaine because it is highly efficacious and has a large safety margin.

Limitations of this study include not standardizing the anesthetic, or surgical procedure; not doing an ANOVA on the pain scores (only morphine consumption was analyzed); and generalizing the findings to all laparoscopic procedures (only women undergoing laparoscopic gynecologic procedures were in this study).

Opioids

Opioids, which have been used as analgesics for centuries, are the most commonly used drugs in the treatment of postoperative pain. Recently, opioids have been used preemptively (Rasanayagam & Harrison, 1996) but with mixed results. A number of studies have examined the combination of opioids and local anesthetics administered epidurally. Although the results of this multimodal approach have been inconclusive and contradictory, there seems to be effective pain control after surgery (Kehlet & Dahl, 1993).

Cabell (2000) investigated whether ketorolac could produce a preemptive analgesic effect in patients undergoing ambulatory laparoscopic gynecologic surgery. Fifty-one women were randomly assigned to one of two treatment groups. Group I (n=25) received intravenous ketorolac (30 mg) upon entrance to the operating room, and intravenous saline at the end of surgery. Conversely, Group II (n=24) received intravenous saline upon entrance to the operating room, and intravenous ketorolac at the end of surgery. Pain intensity in the hospital was measured with a mechanical visual analogue scale (M-VAS), or another name is slide algometer. The researcher or recovery room nurses collected data on admission to the PACU and every 15 minutes for four times, and then every 30 minutes for two times or up to discharge (whichever occurred

first). Twenty-four hours after surgery the patients used a 15 cm VAS to determine their level of pain.

The results of this prospective, randomized, double-blind, placebo-controlled clinical trial showed that patients given ketorolac at the conclusion of surgery (Group II) had significantly lower M-VAS scores. Fentanyl administration (either perioperative or postoperative) was not statistically different between the two groups. However, postoperative fentanyl use, in the PACU, approached a level of significance ($p = .101$). Group I, who received the preemptive medication, had a higher consumption of fentanyl. Also, postoperative oral analgesic use was not statistically significant.

This clinical trial had several limitations due to flaws in the study design. Administering the preemptive ketorolac upon entrance to the operating room did not allow for peak therapeutic levels to be achieved prior to induction or incision. Another limitation was the use of the M-VAS. The initial pain level at times was difficult to obtain from sleepy patients who were recovering from anesthesia. There was a lot of variability in the patient's ability to use the slide algometer, because this tool is completely dependent on alertness. Last, the surgical population underwent multiple laparoscopic gynecologic procedures. Pain characteristics to include type, location, intensity, and duration, can widely vary between the different procedures.

To summarize, six double-blind, randomized, placebo-controlled studies were evaluated in this section. Two NMDA receptor antagonists studies, two local anesthetic studies, and two NSAID studies were reviewed. The clinical investigators of the studies found that preemptive analgesia works in attenuating postoperative pain (regardless of

the drug modality used). However, there does not seem to be any universal answers about the timing or type of agents that are most effective. According to Goodwin (1998), the optimal way to preempt the establishment of pain hypersensitivity may be to apply treatment preoperatively, intraoperatively, and postoperatively.

Further studies need to be conducted in order to examine the timing, and optimal combination of drug administration. Also, further studies need to be conducted to see what drug modalities will yield the best results, as well as have the fewest side effects, and be the most cost-effective. The next two sections will focus on the use of ketorolac and ibuprofen as preemptive analgesics, since they are the two drugs that were compared in this study.

Ketorolac

Ketorolac tromethamine (Toradol) is a NSAID with potent analgesic and moderate anti-inflammatory properties. It is indicated for short-term analgesia because of its pharmacologic profile. Ketorolac's onset of action is about ten minutes after intravenous administration, with peak plasma levels reached in about 50 minutes after a single 30 mg dose. The analgesic effect of ketorolac begins in 30 minutes, and maximum analgesic effect occurs in one to two hours. The duration of analgesia for ketorolac is usually four to six hours (Toradol® package insert, 1997).

Ketorolac was first marketed in the United States in March 1990, and was the first NSAID approved in the United States for intramuscular use (Strom, Berlin, & Kinman, 1996). The Food and Drug Administration (FDA) approved ketorolac in 1995 for intravenous use.

All NSAIDs (ketorolac included) work peripherally by reducing prostaglandin synthesis through the inhibition of the enzyme cyclo-oxygenase which is necessary for the conversion of arachidonic acid to prostaglandins (Fiedler, 1997). Prostaglandins are believed to increase the sensation of pain either by peripheral nerve ending sensitization, or by acting synergistically with other chemical mediators of pain. The following recent research studies on the use of ketorolac in the laparoscopic tubal ligation patient will be examined.

The study by Higgins et al. (1994) looked at the analgesic efficacy of a single dose of ketorolac or ibuprofen when given preoperatively in laparoscopic tubal ligation patients. Fifty women were randomized to receive either ketorolac 60 mg intravenously, ibuprofen 800 mg orally, or placebo. This double-blind, randomized, placebo-controlled study lends support to the proposed research with the researcher's physiological and pharmacological framework. Manipulation of fallopian tubes is thought to induce pain similar to dysmenorrhea, with the latter being associated with increased peritoneal prostaglandins. The ensuing pain can be effectively treated with NSAIDs, and so may be useful analgesics following tubal procedures. In addition, the preemptive use of NSAIDs may inhibit prostaglandin synthesis before tissue injury from surgery, thus preventing the nociceptive impulses.

The results of this study failed to demonstrate a significant reduction in postoperative pain, analgesic requirements, incidence of vomiting, or length of hospitalization after the single preoperative administration of ibuprofen or ketorolac. However, there were several flaws in the design of this study. First, the anesthetic was not standardized, patients either

received succinylcholine or vecuronium for tracheal intubation. Succinylcholine is known to cause muscle aches postoperatively due to the fasciculations that can occur after administration. Second, the surgical technique was not standardized, either Falope rings or chromic endoloops were used. Third, an oral gastric tube was inserted, and the stomach was decompressed immediately after the surgical procedure, meaning some of the oral ibuprofen may have been removed from the gut. Fourth, the administration of the oral ibuprofen was only 30 minutes prior to incision, which did not allow for the drug to peak prior to incision. Last, a post hoc power analysis revealed that at least 20 subjects per group was needed in order to determine a significant difference in VAS scores.

Cade and Kakulas (1995) compared ketorolac 30 mg IM to meperidine 100 mg IM, both given intraoperatively to women undergoing laparoscopic sterilization. Both drugs were given after induction in a randomized, double-blind fashion to sixty subjects. While both drugs had comparable analgesic effects in the immediate postoperative period, ketorolac had significantly better results approximately 4 hours after surgery. The ketorolac group members had significantly lower pain scores (p=0.006), required less time to awake (p=0.01), ambulated sooner (p=0.0005), were discharged sooner (p=0.02), and had fewer unplanned admissions (p=0.01).

The researchers concluded that ketorolac served as a useful supplement for analgesia following laparoscopic sterilization. There were two main weaknesses in this study's design. The study drugs were given after induction; meaning that the drugs did not have time to peak prior to incision, and the study lacked information on the type/types of tubal occlusion used.

Ketorolac Side Effects

Ketorolac has been recognized as a potent NSAID for relief of moderate to severe pain. However, it has been associated with a number of unfavorable side effects. The following will reveal some of the affiliated risks and clinical considerations when using ketorolac.

Strom et al. (1996) conducted a retrospective cohort study that used data from the records of 9900 patients. The researchers examined the effects of ketorolac on gastrointestinal bleeding and operative site bleeding. The latter aspect of this study also considered the suppression of platelet function resulting from ketorolac's inhibition of prostaglandins. They concluded there is an increased risk of gastrointestinal bleeding and operative site bleeding with higher doses of ketorolac in the elderly, and when used for more than 5 days. Avoiding these increased risk areas should improve the risk-benefit balance when giving ketorolac to patients (Strom et al., 1996).

Hennessy and Kinman (1997) reviewed 10,272 courses of ketorolac therapy and 10,247 courses of parenteral opioid therapy. They examined the data looking for possible hepatotoxic effects related to ketorolac use. The study was unable to isolate supporting evidence of hepatotoxic effects related to ketorolac administration. The researchers concluded that short-term ketorolac use was not associated with liver injury.

Feldman et al. (1997) also conducted a retrospective cohort study that assessed the risk for acute renal failure with the use of ketorolac. Prostaglandin inhibition by ketorolac circumvents the vasodilatory effects on renal arteries, and could theoretically decrease renal perfusion. Data was collected for 21 months on patients who received parenteral

ketorolac (with or without concomitant opioid use) or opioids only. The operational definition for acute renal failure was a serum creatinine that was greater than baseline by 50% plus an absolute increase relative to the baseline concentration. Also, a secondary definition (along with the laboratory data) was documentation of acute renal failure in the hospital chart.

The experimental group was comprised of 9850 subjects while the control group had 10145 subjects. They noted that the events of acute renal failure occurred later for the ketorolac group as compared to the opioid group. Their analysis suggested that prolonged administration of ketorolac (more than 5 days) may be associated with higher occurrence of acute renal failure if the patient had any of the identified predisposing conditions (congestive heart failure, chronic renal disease, cirrhosis, and uncontrolled hypertension). They concluded that ketorolac was as safe for patients as opioid narcotics if administered for short-term therapy (less than five days). For the purpose of this study, we excluded subjects who presented with congestive heart failure, acute renal failure, chronic renal disease, cirrhosis, or uncontrolled hypertension.

In summary, the treatment of postoperative pain by the preemptive administration of NSAID's has received increased interest in recent years. Ketorolac has been examined in numerous clinical trials due primarily to its opioid-sparing effects and availability in parenteral formation. However, ketorolac is not without its own set of adverse side effects, and must be used very judiciously or altogether avoided in certain patient populations. The preceding studies have elicited varied results pertaining to ketorolac's

appropriate application and efficaciousness. However, since its approval by the FDA for intravenous use, it has become a favored analgesic among healthcare providers.

Ibuprofen

Ibuprofen is a NSAID that is widely used due to its excellent analgesic and antipyretic effects as well as the relatively low number of side effects. It is used in the treatment of primary dysmenorrhea, arthritis, migraines, and muscle and tendon injuries. Also, it is commonly used for prophylactic pain relief before certain procedures (Burke, 1996).

Ibuprofen (when administered orally) has an onset of action in 30-60 minutes, duration of action is four-six hours, and time to peak serum concentration is within one to two hours (Donnelly, Cunningham, & Baughman, 1998). Ibuprofen was developed in the 1960's, and has been used as a prescription drug since 1967 in Great Britain, and since 1974 in the United States. The FDA approved ibuprofen for nonprescriptive use in adults in 1984, and in children in 1989 (Davies, 1998).

Ibuprofen (like ketorolac) is a potent inhibitor of prostaglandin synthesis, and the mechanism of action of ibuprofen is the same as ketorolac in that it inhibits central and peripheral prostaglandin synthesis (Kepp, Sidelmann, & Hansen, 1997). This mechanism of action blocks the cyclooxygenase pathway in the arachadonic acid cascade. Blocking cyclooxygenase results in both analgesic and anti-inflammatory effects.

Side effects of ibuprofen are few, but include gastrointestinal distress, prolonged clotting time, headache, and dermatological reactions. Ibuprofen should be used with caution in patients with cardiac, hepatic, or renal dysfunction, and in patients taking

coumadin, methotrexate, furosemside, thiazide diuretics, or lithium. Ibuprofen is contraindicated in the third trimester of pregnancy because it may delay parturition, promote postpartum bleeding, and promote early closure of the ductus arteriosis in the fetus (Burke, 1996). There are many studies in the literature on ibuprofen, but not all of the studies are relevant to the tubal ligation patient, or to the theory of preemptive analgesia. The following is a review of ibuprofen in the literature, which is pertinent to the tubal ligation patient.

Ibuprofen has been shown to be effective in the treatment of primary dysmenorrhea. The postoperative pain accompanying a bilateral tubal ligation has been likened to dysmenorrhea. Therefore, treatment of this type of postoperative pain with ibuprofen logically follows. Pedron, Gonzales-Unzaga, and Medina (1998) did a six month long prospective study to assess the effectiveness of prophylactic ibuprofen in the treatment of severe and disabling dysmenorrhea refractory to previous treatment. Fifteen subjects began to take ibuprofen 400 mg every eight hours, 24 hours prior to the onset of menses, and continued during four days of menstruation for six consecutive cycles.

The results showed a statistically significant progressive decrease in the pain rating during the duration of the treatment. The authors concluded that ibuprofen is an effective treatment for selected women with severe and disabling dysmenorrhea. The generalizability of this study is limited because the women included in the study were limited to those who were sexually inactive and had regular menstrual periods along with severe, disabling dysmenorrhea. A threat to the external validity of this study is the

Hawthorne effect, especially since there was no control group. The subjects may have had progressive decreases in the amount of pain just from being followed for six months.

Multiple studies have been conducted in the use of ibuprofen as a postoperative analgesic for various types of surgeries, including bilateral tubal ligation, and other abdominal gynecological surgical procedures. The following two studies were conducted to examine ibuprofen's efficacy in patients undergoing surgical procedures.

Sunshine, Olson, O'Neil, Ramos, and Doyle, (1997) conducted a study comparing the effectiveness of ibuprofen in combination with hydrocodone as compared to plain ibuprofen. This study looked at the treatment of acute postoperative pain after cesarean section or gynecological surgery in a hospital in Puerto Rico. One hundred and twenty patients were randomly assigned to receive one of three treatments; 15 mg hydrocodone bitartrate with 400 mg ibuprofen, 400 mg ibuprofen, or placebo.

The investigators found in this double blind, parallel-group clinical trial the addition of 15 mg of hydrocodone to ibuprofen 400 mg provides significantly more analgesia than 400 mg ibuprofen alone. Including a placebo group in this study's design raises some ethical concern, because the subjects in the placebo group did not receive anything for pain. In this study, if the subjects requested additional pain medication they were dropped from the study, and then their last observed pain intensity difference score was carried forward for all time measurements subsequent to their re-medication.

Thirty-two of the placebo patients (82%) and ten (25%) from the ibuprofen alone group were remedicated. None of the patients treated with the hydrocodone/ibuprofen group needed remedication. One subject out of the 120 dropped from the study after

receiving the (placebo) study drug. This study would not be reproducible in most institutions due to strict protection of human subjects. Most internal review boards would not allow a study to be conducted if a group of subjects would not be receiving pain medication postoperatively. This study was valuable in that the researchers did find that the addition of hydrocodone to ibuprofen was more efficacious in decreasing postoperative pain then ibuprofen alone.

Mixter, Meeker, and Gavin (1998) conducted a study with 70 subjects (18 to 83 years old) undergoing laparoscopic transperitoneal inguinal herniorrhaphy under general anesthesia. In this double blind, prospective, randomized study ibuprofen was compared to ketorolac. Group One received a placebo capsule one hour before surgery and ketorolac, 60 mg intravenously, at the time of trocar insertion. Group Two received ibuprofen, 800 mg an hour before surgery, and normal saline, 2 ml intravenously, at the time of trocar insertion. The pain management in this study included the administration of ibuprofen every six hours postoperatively even in the absence of pain.

The authors found that ibuprofen was as effective as ketorolac in reducing the amount of narcotic administered in the PACU. Also, there was no significant difference in the level of pain experienced at the time of discharge, at 18 hours, and at 24 hours postoperatively. The study design had the following limitations: The anesthetic was not standardized. There was no control group, and the administration of ketorolac occurred after the trocar insertion. The authors justified not having a control group, because they felt it would be wrong not to give the patients one of the nonsteriodal drugs. They stated

that it would be very hard to have a placebo control group in their study, because they had such a successful program using NSAIDs preemptively in their clinic.

In summary, of the three studies examined in this section on ibuprofen, two did not have placebo-control groups (one because of ethics). In the one study that had a placebo-control group, the patients were dropped if they requested rescue pain medication. Ibuprofen was found to be effective in decreasing dysmenorrhea, and in the study by Mixter et al. (1998) ibuprofen was shown to be as effective as ketorolac in decreasing postoperative pain.

Conclusion

Over an extended period of time ibuprofen and ketorolac studies have shown both NSAIDs to be efficacious in the treatment of pain and inflammation produced by disease processes, injuries, and surgical procedures. Ibuprofen has been proven to decrease the amount of pain associated with primary dysmenorrhea. The postoperative pain of bilateral tubal ligation has been compared to that of dysmenorrhea. So it logically follows that ibuprofen or ketorolac would be a good analgesic choice in the treatment of postoperative pain after bilateral tubal ligation. The literature is varied on which of the NSAIDs is more effective when administered preemptively. Mixter et al. (1998) found ibuprofen and ketorolac to be equally effective. Conversely, Higgins et al. (1994) found the opposite to be true (neither drug was effective).

Flaws in study design accounted for the majority of variability in the results found during this literature review. Limitations in the studies included: Administering the NSAIDs in a fashion that peak therapeutic levels were not achieved prior to induction or

incision. Often anesthetics and surgical procedures were not standardized. Data collection sometimes did not start until the patients were leaving the PACU, and did not continue once the patients were discharged home. Analysis of pain location, and in a few of the studies, intensity was not carried out. The current study incorporated some of the strengths and avoided some of the limitations found in the literature in order to have a strong, tightly controlled study design. This study investigated and compared the effectiveness of the pre-emptive use of ibuprofen and ketorolac on postoperative pain, opioid usage, and elapsed time until first rescue administration following ILBTS.

CHAPTER III

Methodology

This was a prospective, double-blind, randomized, clinical trial comparing the difference between the NSAIDs ketorolac and ibuprofen in preempting postoperative pain in patients presenting for ILBTS. This chapter describes the population, sample, setting, instrumentation, study design, procedure for data collection and analysis, and protection of human subjects.

Population, Sample, and Setting

The sample population was derived from female patients electing to undergo ILBTS. The setting was Tripler Army Medical Center (TAMC), a 256 bed regional medical center, with thirteen surgical suites, located on the island of Oahu in the State of Hawaii. TAMC provides all major surgical services (including gynecological) for members of all branches of the United States military (Army, Air Force, Navy, Marine, & Coast Guard). This includes (a) active duty military and their dependent family members, (b) military retirees and their dependent family members, and (c) Veteran's Affairs (VA) eligible patients. In addition, TAMC provides referral services to all other military facilities in the Pacific region. Lastly, TAMC is a teaching facility that provides residency training in a variety of surgical specialties, to include obstetrics and gynecology.

Subjects were screened and a convenience sample consisting of those meeting the inclusion criteria and not exclusion criteria were invited to participate in the study. Inclusion criteria consisted of (a) women of at least 18 years of age presenting for

elective ILBTS from November 3, 1999 to June 30, 2000. (b) American Society of Anesthesiologists (ASA) category I or II, and (c) at least six weeks postpartum.

Exclusion criteria (Appendix B) was based on the associated co-morbidities for both ketorolac and ibuprofen. Prospective patients were excluded for the following reasons if either noted during their history and physical exam or during the preoperative anesthesia interview: (a) a history of allergy to NSAIDs or aspirin, (b) a history of peptic ulcer disease or asthma, (c) a history of bleeding abnormalities or current use of anticoagulant or anti-platelet drugs, (d) a history of renal or hepatic dysfunction, (e) a history of psychiatric illness or substance abuse, (f) subjects who had taken aspirin in the past ten days or NSAIDs in the past eight hours, (g) non-English speaking subjects, (h) a reported body weight of less than 50 kg (related to the manufacturer's recommended dosing), and (i) a clinical indication for using succinylcholine with induction or placement of an oral gastric tube for stomach decompression.

A minimum sample size of 20 subjects per group was used based on a post hoc power analysis of the study by Higgens et al.(1994) using SamplePower v1.2 (SPSS, Inc.). The main effect of drug differences observed between ketorolac and ibuprofen yielded a medium effect size of 0.25 and a power of greater than 0.80 with 20 subjects per group.

The study subjects were randomly assigned to one of two groups. Group I consisted of patients receiving oral ibuprofen 800 mg and intravenous normal saline preoperatively. Group II received an oral placebo and ketorolac 30 mg intravenously. Omission of a placebo control group was based on the review of literature suggesting that

there is a difference between preoperative NSAIDs and a placebo control (Brodie & Casper, 1987; Cade & Kakulas, 1995; Comfort, et al., 1992; DeAndrade, et al., 1994; O'Hanlon, et al., 1996). In view of these findings and current clinical practices by anesthesia providers at TAMC, we felt that the advantages of postoperative pain control, recovery time, and cost effectiveness to the facility superceded the use of a placebo control group. The study by Mixter et al. (1998) provides support for this decision.

Instrumentation

We used an 11 point verbal Numeric Rating Scale (NRS) as the tool for measurement of postoperative pain reported by the patients. The Agency for Health Care Policy and Research, (which has guidelines published regarding acute pain management in adults) has recommended using the NRS (Dalton & McNaull, 1998). Strong correlations have been reported between the Visual Analogue Scale (VAS) and the NRS in studies dating over 20 years old (Ohnhaus & Adler, 1975; Woodforde & Merskey, 1972). In addition, the NRS is considered to have good reliability and construct validity when patient self-report is used as the method of data collection (Briggs, Closs, & Mphil, 1999). The NRS was previously established in the unit protocols for the PACU and the ASC in the facility where the study was conducted. This fostered the support received from the nursing staff who assisted with data collection. In addition, an investigator designed demographic data collection sheet (Appendix C) was used.

Numeric Rating Scale

The reliability of an instrument is the consistency with which it measures what it is supposed to measure (Polit & Hungler, 1995). Ferraz et al.(1990) used the test-retest

method to assess the reliability of the NRS, the VAS, and the Verbal Rating Scale(VRS) in two groups (literate and illiterate) of patients with rheumatoid arthritis. A convenience sample of 91 outpatients, seen in a rheumatology clinic, was studied. The investigators had the patients rate their pain on the three scales, the NRS, the VAS, and the VRS at two different times. They rated their pain on all three scales, presented in random order before their outpatient appointment and again after their appointment. The investigators inserted the medical appointment between the two data collection points to minimize carryover effect.

The investigators found that the NRS has higher reliability in both groups than the VAS or the VRS. The Pearson product correlation between the first and second assessment was 0.963 in the literate group and 0.947 in the illiterate group. Although the subjects in our study were not illiterate, they were emerging from general anesthesia and therefore may have had trouble reading as well as writing or making a mark on a line. Additionally, some of the subjects did not have their corrective lenses in the immediate postoperative period, making it difficult to read. Because our subjects were unable to read temporarily, we felt the Ferraz et al. (1990) study was pertinent to postoperative patients. Therefore, the NRS was a reliable tool to use with this sample.

Validity of an instrument refers to the degree to which it measures the attribute that it is supposed to measure (Polit & Hungler, 1995). One method of establishing the validity of an instrument is to compare it to an instrument with established validity. Paice & Cohen (1997) studied a convenience sample of 50 subjects that met three criteria: (a) documentation of malignancy, (b) current experience of pain, and (c) ability to

understand English. Each subject rated his or her pain on the VAS, the NRS and the simple descriptor scale. After rating their pain, they indicated which scale they preferred. The NRS was the preferred scale. The investigators used Spearman correlation coefficients to establish the similarity between the three pain intensity scales, providing evidence for convergent validity. A strong positive correlation between the VAS and the NRS also was shown to be statistically significant ($r = 0.847$, $p < 0.001$). The strong correlation between the VAS and the NRS supports the validity of the NRS. This tool allowed us to be consistent in our data collection even when collecting data telephonically.

An explanation of the NRS was initially given to the subjects, by one of the investigators, using a standardized script. This was done either telephonically, at least one day before surgery, or during the preanesthesia interview. The subjects were asked to give a return verbal understanding of the tool. In order to establish a baseline on each study participant, the first NRS was administered the morning of surgery.

A member of the Surgical Admissions Center (SAC) nursing staff asked the study participants to rate any pain they were having using the NRS. All of the personnel in the SAC received training on the NRS prior to the start of the study. The subjects were asked to rate their pain using the NRS seven more times. The times were as follows: (a) immediately upon arrival to PACU, (b) fifteen minutes after arrival to PACU, (c) one hour after surgery or discharge from PACU (whichever came first), (d) two hours after surgery, (e) three hours after surgery or discharge home (whichever came first), (f) six

hours after surgery, and (g) at bedtime on the day of surgery. None of the subjects had pain prior to surgery, so that NRS score was dropped from data analysis.

Procedure for Data Collection

The following procedures were used for data collection:

1. Prior to the start of the study, a pharmacist was assigned to assist the investigators with any pharmacy-related issues. An initial goal prior to commencement of data collection was design of a packaging system that would allow the study to be double-blinded with regard to the drugs under investigation. The intravenous ketorolac (30 mg or 1 cc) and saline (1 cc) placebo were easily packaged in 3 cc syringes; the contents were not discernible to the investigators.

The packaging of the ibuprofen proved to be more challenging. At first the investigators/pharmacist explored the possibility of using a single placebo pill that would resemble the 800 mg ibuprofen tablet; however, the pharmacy was unable to find a placebo meeting this criteria. Subsequently, one of the manufacturers of ibuprofen was approached with the premise of crushing an 800 mg tablet and placing it in a gelatin capsule. According to the manufacturer, ibuprofen has decreased bioavailability when exposed to air; therefore this approach was abandoned. The use of an elixir was also explored, but was rejected by the investigators related to the amount of particulate liquid that the subjects would have to drink just one hour prior to induction (approximately 60 ml, which would have been a safety-related issue). The final design was to use four 200 mg over-the-counter ibuprofen tablets; each placed inside a gelatin capsule. Similarly, four placebo gelatin capsules were used as the placebo. Inadvertently, the pharmacist

prepared 60 study drug packets, instead of the requested 50. This proved beneficial as 58 packets were utilized due to higher than anticipated subject attrition. Additionally, one of the pharmacists assisting the investigators developed a computerized medication order set, formulated a pharmacy budget, and produced a study drug information teaching packet with access on the facility's intranet website. All personnel involved in the handling of the study drugs were required (JCAHO standard) to read the information in the aforementioned packet and take a product knowledge quiz.

2. All patients scheduled for ILBTS at TAMC between November 1,1999 and June 30, 2000 were contacted by one of the investigators, at least one day before surgery. Potential candidates for the study were identified on the facility's intranet surgery scheduler/roster; prospects were either contacted at home by telephone, or if possible at their preoperative anesthesia interview in the SAC. Those candidates who met inclusion criteria, and did not fall under exclusion criteria were asked to participate in the study.

3. If possible, written, informed consent (Appendix D) was obtained from subjects at their preanesthesia interview. Otherwise, verbal consent was obtained telephonically, and then written, informed consent was obtained on the day of surgery in the SAC.

4. After obtaining subjects' consent, a medication order set (Appendix E) was sent to the pharmacy one day in advance of surgery; in addition, the pharmacy was contacted to verify receipt of the order. The pharmacist, assigned to work with the investigators, randomly assigned the subjects to one of two groups. This was accomplished using a standard table of random numbers.

5. On the day of surgery, one of the investigators picked up the study drug packet in the pharmacy, and placed the packet along with the data collection sheet, volunteer affidavit, and the home questionnaire (all forms were a lime green) on the subject's chart in the SAC.

6. The subjects' charts were labeled with a yellow "BTL study patient" to indicate participation in the study.

7. Upon admission to the SAC written, informed consent (if not already done) was obtained from the subjects by one of the staff nurses. The NRS was once again explained to the subject with a return verbal demonstration of the tool.

8. The subjects were asked to rate any preoperative pain using the NRS, and this was recorded along with age, weight, height, menstrual status, and ethnicity on the data collection sheet.

9. Approximately one hour prior to induction, the subjects were given either ibuprofen 800 mg or an oral placebo. The investigators as well as the subjects were blinded as to which medication was given.

10. Soon after arriving in the preoperative holding area, an intravenous line was placed in either the subject's hand or forearm with Lactated Ringers as the maintenance solution.

11. Following placement of a peripheral intravenous line (approximately 15 minutes prior to induction), subjects receiving ibuprofen were given an intravenous placebo. Conversely, subjects receiving an oral placebo received ketorolac 30 mg intravenously.

12. Intravenous midazolam (1-5 mg) was administered for anxiolysis.

13. The subjects were then transported to the operating room.

Standardized Anesthetic

Induction

1. Monitoring devices were applied to include: (1) continuous EKG, (2) noninvasive blood pressure cuff, (3) precordial stethoscope, (4) pulse oxymeter, (5) oxygen analyzer, (6) capnograph, (7) peripheral nerve stimulator, and (8) temperature monitor.

2. The subjects were preoxygenated/denitrogenated with 100% oxygen.

3. Fentanyl 50-150 mcg intravenously was given to attenuate the sympathetic response to intubation.

4. Propofol 2-3 mg/kg intravenously was used for induction of anesthesia.

5. The ability to manually ventilate was established prior to paralysis.

6. Neuromuscular blockade was achieved using rocuronium 0.6-1.2 mg/kg.

7. The subjects were intubated by direct laryngoscopy.

Maintenance

1.The inspired oxygen fraction was maintained at a minimum of 0.30 with air and oxygen.

2. Anesthesia was maintained with an end-tidal concentration of sevoflurane (0.5-3%) titrated to effect.

3. The autonomic response to surgical stimuli was attenuated with inhaled agent and fentanyl 25-50 mcg, titrated to effect. Total fentanyl administration including the induction dose was limited to 5 mcg/kg.

4. Dolasetron 12.5 mg was given intravenously before emergence.

Emergence

1. Reversal of neuromuscular block was accomplished with neostigmine .04-.08 mg/kg, and glycopyrrolate 0.01- 0.02 mg/kg intravenously (equivalent volumes).

2. The subjects were extubated in the operating room when awake, and after extubation criteria had been met.

3. The subjects were transported to the PACU with supplemental oxygen at six liters per minute via simple face mask.

Postoperative Assessment

1. The anesthesia care provider accompanying the subjects to the PACU asked them to rate their pain using the NRS on arrival to the unit.

2. The Post Anesthesia Care Unit (PACU) nursing staff had the subjects evaluate their pain using the NRS at 15 minutes after admission.

3. The subjects' pain was subsequently evaluated using the NRS every hour and on discharge.

4. The subjects were discharged from the PACU (Appendix F) and the SAC (Appendix G) per protocol.

5. The subjects were given a "take-home" questionnaire to score their pain at six hours and at bedtime postoperatively (Appendix H).

6. While in the PACU, rescue analgesics and antiemetics were administered per unit SOP (Appendix I). While in the SAC, rescue analgesics and antiemetics were administered per unit SOP (Appendix J).

7. Approximately 24 hours after surgery, one of the investigators contacted each subject by telephone to obtain the six- hour and bedtime NRS scores.

8. A pilot study was conducted using the first six subjects.

Protection of Human Subjects

The research study was approved by the Scientific Review Committee and the Human Use Committee of TAMC (Appendix K). Also, the Committee for the Protection of Human Subjects (CPHS) at the University of Texas at Houston Health Science Center (page ix) granted approval.

Subjects were verbally counseled at least one day prior to surgery, and consent was obtained prior to entering the patients in the study. Subjects were informed that their participation was entirely voluntary, and that they could withdraw from the study at any time. The purpose of the study, as well as risks, benefits, and the subjects' time commitment were discussed.

Confidentiality was maintained as recommended by Polit and Hungler (1995). A number identified each subject, and the data were entered into a computer using only this number to identify the subject. The investigators secured the information maintained in a database (on floppy computer diskettes kept in a locked file). Information linking the subjects' data with their name was maintained separately, and was only accessible to the researchers and faculty. In addition, the pharmacy maintained a log, which cross-referenced subjects names and registrar numbers with study packet number in a locked file. This information was readily available in the case of a medical emergency.

Only aggregate information is being disclosed. No individual data will be reported. Subjects that desire the results of the study will be sent a copy of a summary of the results, after thesis defense. Addresses were maintained separately from the data in the locked file, and were destroyed after results are sent to the participants and the thesis was defended.

Study Design

This was a prospective, double-blind, randomized, clinical trial testing the preemptive effects of two different NSAIDs on postoperative pain, total opioid administered postoperatively, and elapsed time until first rescue medication was administered. A total of 58 subjects participated; viable data was available on 44 subjects after attrition.

Internal and External Validity

One threat to the internal validity included selection bias implied by the use of a convenience sample. Randomization yielded some degree of equalization between groups (Polit & Hungler, 1995). We controlled for instrumentation by giving identical training to all the staff who were data collectors and by scripting the dialog with the subject. In order to obtain the NRS scores at six hours after surgery and bedtime, the investigators educated the subjects on the importance of the follow up telephone call and obtained an alternate phone number to contact them. The take home questionnaire was printed on lime colored paper to assist with easy identification among the other perioperative forms. A self-addressed stamped envelope was included so the participants could conveniently return-mail the questionnaire following completion.

Attrition may be due to unanticipated changes in the surgical procedure, anesthetic protocol violation, inability to provide data due to excessive postoperative sedation, or inability to reach the subjects 24 hours after surgery by telephone. Furthermore, subjects may request removal from the study. This threat to internal validity was addressed by the study protocol standardizing the surgical procedure, anesthesia, and all medication administered to the patient. In an effort to minimize mortality resulting from the inability to obtain "at home" NRS scores, we counseled the patients of the importance in returning the written questionnaire, in addition to data received during the follow-up telephone call.

One threat to external validity is the study's lack of a placebo control group. Omission of a placebo control group was based on the review of literature suggesting that there is a difference between preoperative NSAIDs and a placebo control (Brodie & Casper, 1987; Cade & Kakulas, 1995; Comfort, et al., 1992; DeAndrade, et al., 1994; O'Hanlon, et al., 1996). In view of these findings and current clinical practices by anesthesia providers at TAMC, we felt that the advantages of postoperative pain control, recovery time, and cost effectiveness to the facility superceded the use of a placebo control group. The study by Mixter et al. (1998) provides support for this decision.

However, we have a comparison group, which is the closest that we can come to a placebo control in this type of study. Due to the assumption that NSAIDs provide preemptive analgesia, the study yields results comparing one drug to another and postoperative pain. There was no query into the efficacy of preemptive analgesics.

We minimized the Hawthorne effect by using a double-blind design. Having a scripted dialog with the subject attempted to minimize the experimenter effect. Our data

collection procedure enumerated in detail in order to allow for exact replication, therefore decreasing the chance of experiencing the measurement effect.

Data Analysis

Demographic data was analyzed using descriptive statistics, Chi-Square (ethnicity, bupivicaine drops administered), Fisher's exact test (ASA category), and Student's t-test (age, BMI, height, weight, length of surgery, elapsed time following drug/placebo administration until direct laryngoscopy/incision/occlusion of first tube). NRS scores were analyzed using a two-way repeated measures ANOVA with orthogonal contrasts. A Pearson's Correlation test was used to look for correlations among the data. A difference was considered significant by convention with $\alpha \leq 0.05$. Statistical Products and Solutions Software (SPSS) was used by the investigators to analyze the data. A statistician reviewed the data and assisted with the analysis. Content analysis was done on qualitative data by analyzing raw data and developing major categories for each question. An experienced qualitative investigator worked with the investigators to insure inter-rater and intra-rater reliability.

Chapter IV

Analysis of the Data

The purpose of this study was to compare postoperative pain scores in female patients presenting for ILBTS with general anesthesia when they received either ibuprofen orally or ketorolac intravenously before surgical incision. The two study groups are compared in this chapter with regard to demographic characteristics and research findings. Our investigation had three hypotheses: (a) There would be a difference in reported postoperative pain, (b) there would be a difference in the amount of opioid administered postoperatively, and (c) there would be a difference in the elapsed time until administration of the first rescue medication. Study findings supported rejection of the first null hypothesis: There will be no difference in reported postoperative pain scores in patients undergoing ILBTS who preemptively receive either ketorolac 30 mg intravenously or ibuprofen 800 mg orally.

Description of the Sample

Sixty-eight women presented for elective ILBTS during the eight-month data collection period; our final sample consisted of 44 ASA category I and II patients. Data collection ended after determining that viable data had been obtained from the 44 subjects. Subject attrition was related to the following. Ten prospective subjects were not enrolled due to eight meeting exclusion criteria and two choosing to not participate in the study (see Table1). Therefore, our rate of capture was 85.3% for the patients who presented for ILBTS during the data collection period.

Table 1

Convenience Sample Capture Data (N=10)

Exclusion Criteria for Patients Not Enrolled in Study	Frequency
Does not understand English	0
Less than 18 years old	0
Weighs less than 110 pounds	1
Allergic to NSAIDs or aspirin	2
History of asthma	3
History of liver problems	0
History of kidney problems	0
History of bleeding ulcers	0
Aspirin use within the last 10 days	0
History of psychiatric illness	0
Less than six weeks postpartum on the day of surgery	0
Clinical indication for intubation requiring succinylcholine	2
Patient refusal	2
Total	10

Six subjects were removed from the study secondary to several causes (see Table 2). The attrition rate for the study was 12.0%.

Table 2

Patients Disenrolled From The Study (N=6)

Reason for Disenrollment	Frequency
Additional procedure performed	3
Hx acute pain	1
Protocol violation	1
Hcg positive on morning of surgery	1
Total	6

Also, eight additional study packets were counted and discarded due to the following: (a) Six patients returned at a later date following cancellation (by the patient) and rescheduling of their surgery, (b) one patient was rescheduled after their case was cancelled due to the OR suite running late, and (c) one patient had two drug packets prepared by the in-patient pharmacy.

Participants enrolled in the study were assigned to one of two groups by inpatient pharmacy personnel using a table of randomization. Group I received 800 mg ibuprofen orally in the SAC (4 gel caplets with a 200 mg ibuprofen tablet inside) and a 1 ml intravenous placebo immediately after placement of a peripheral intravenous catheter (see Table 3). Conversely, Group II received an oral placebo in the Surgical Admission Center (4 gel caplets) and ketorolac 30 mg intravenously immediately after placement of a peripheral intravenous catheter (see Table 3). The study participants, investigators, and nursing staff who assisted with data collection were blinded to the actual study drugs/placebos given to the patients.

Demographic data was analyzed using descriptive statistics, Chi-Square (ethnicity and bupivicaine drops administered), Fisher's Exact test (ASA category), and Student's t-test (age, BMI, height, weight, length of surgery, elapsed time following drug/placebo administration until direct laryngoscopy/incision/occlusion of first tube). NRS scores were analyzed using a two-way repeated measures ANOVA with orthogonal contrasts.

Homogeneity between the two groups was tested with regard to demographic characteristics. Areas examined included age, height, weight, BMI, LMP, ethnicity, and ASA classification (Table 3). They were similar in all aspects; however, three variables (LMP, nausea in hospital, and ASA classification) *approached* a statistical significance (p=0.053, p=0.065, and p=0.064 respectively).

Table 3

Demographic Data Comparing the Two Groups (N=44)

Demographic Data	Group I (n=23)	Group II (n=21)	Probability
Age (years)	31.6 ± 5.73	31.2 ± 6.15	0.82
Height (cm)	162.8 ± 10.77	163.6 ± 9.82	0.818
Weight (kg)	70.7 ± 11.33	66.24 ± 10.79	0.186
Body Mass Index	27.07 ± 4.91	24.87 ± 3.21	0.09
*^LMP (days)	14.9 ± 2.85$^{\sigma}$	23.7 ± 3.33$^{\sigma}$	0.053
Ethnicity			
Caucasian	14 (61%)	14 (67%)	N/A
African-American	8 (35%)	5 (24%)	N/A
Asian/Pacific Islander	1 (4%)	2 (10%)	N/A

*ASA Classification			
I	19 (82.6%)	12 (57.1%)	> **0.064
II	4 (17.4%)	9 (42.9)	
*Nausea in hospital	9 (39.1%)	3 (14.3%)	0.065
Received antiemetic(s)	7 (31.8%)	3 (14.3%)	0.174

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

* Denotes approached a level of significance.

** Reflects the probability for distribution of ASA category I or II patients into one of the two treatment groups.

^ Subjects receiving Depo-Provera® or who were postpartum were treated as missing data points.

$^{\sigma}$ Reflects standard error of the mean.

Variables for the surgical procedure and anesthesia were also similar between the two groups (Table 4). There were no statistically significant differences in the total doses of versed, fentanyl, propofol, rocuronium, sevoflurane, neostigmine and robinul; this was attributed to strict adherence to established protocol.

Table 4

Surgical Procedure and Anesthetic Variables (N=44)

Variables	Group I (n=23)	Group II (n=21)	Probability
Elapsed time until direct laryngoscopy following oral/placebo drug (min)	64.9 $\pm$ 4.39	67.6 $\pm$ 5.11	0.69

Elapsed time until direct laryngoscopy following intravenous/placebo drug (min)	17.1 ± 1.63	16.3 ± 1.72	0.75
Elapsed time until incision following oral/placebo drug (min)	93.0 ± 24.04	96.7 ± 23.50	0.612
Elapsed time until incision following intravenous/ placebo drug (min)	45.3 ± 9.41	45.0 ± 8.27	0.909
Elapsed time until first tube occluded after oral/ placebo drug (min)	111.2 ± 29.0	112.9 ± 25.9	0.845
Elapsed time until first tube occluded after intravenous/placebo drug (min)	65.0 ± 15.62	60.7 ± 12.49	0.314
Total surgery time (min)	39.1 ± 17.66	38.4 ± 16.07	0.898
Total PACU time (min)	69.7 ± 27.80	67.6 ± 26.27	0.804
Total postoperative time until discharge (min)	256.3 ± 99.43	254.4 ± 90.00	0.947
Total intraoperative fentanyl used (mcg/kg)	4.38 ± .707	4.34 ± .874	0.869
Total rescue morphine (mg)	4.35 ± 5.50	5.71 ± 7.12	0.478

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

There were no significant differences following preemptive medications or placebos for elapsed times until direct laryngoscopy, surgical incision, or occlusion of tubes using Falope Rings. Length of surgery and rescue medication for pain control was

also similar for the two groups. Three patients in Group I and four patients in Group II received meperidine postoperatively. Morphine equivalents were calculated (Demerol® 10 mg = morphine 1 mg) in order to complete statistical analysis (Stoelting, 1999). With regard to the occlusive technique, one subject's fallopian tubes were cut and tied, one had Hulka clips applied, and lastly, one also had bipolar electrocoagulation performed. There was no difference statistically when the data was subsequently analyzed without the aforementioned three participants. Therefore, we retained them in the study. Lastly, three study participants were admitted overnight for the following reasons: (a) One for pain refractory to oral medication in Phase II recovery, (b) one who had adhesions and was being observed for bleeding following development of a hematoma postoperatively, and (c) one who did not have an escort available after meeting discharge criteria in Phase II recovery. We were able to retain the three aforementioned participants, as pain scores were assessed through bedtime and they completed their "take-home" questionnaires. Also, no significant differences were revealed between the two groups when their NRS scores were excluded from data analysis.

Findings

Data Analysis

The tested hypothesis states the following: Patients who receive a preemptive dose of ibuprofen 800 mg orally will have different reported postoperative pain scores, required postoperative opioid usage, and elapsed time until first rescue medication than those patients who received a preemptive dose of ketorolac 30 mg intravenously. Pertinent data, which included the aforementioned variables were collected and

documented by blinded observers using a preprinted data collection tool (Appendix C). Both groups had baseline mean pain scores (i.e., recorded upon admission to the hospital and before surgery) of zero. Following analysis with a one-way ANOVA, there was no difference between the two groups with regard to amount of postoperative opioid usage or elapsed time until administration of the first rescue medication.

Postoperative pain was assessed using a verbal NRS as follows: arrival to the PACU, 15 minutes after arrival, at hourly intervals until discharge home or 3 hours later whichever came first, 6 hours after the end of surgery, and finally at bedtime. NRS scores were analyzed statistically with a two-way repeated measures ANOVA using orthogonal contrasts. Stated more succinctly, the orthogonal contrasts compare a weighted average of the means of the meaningful subdivisions of the total variation of the treatments. Therefore, the 2 groups were compared using an orthogonal contrast of the NRS responses of the last 4 periods (2 hours postoperatively through bedtime), and an

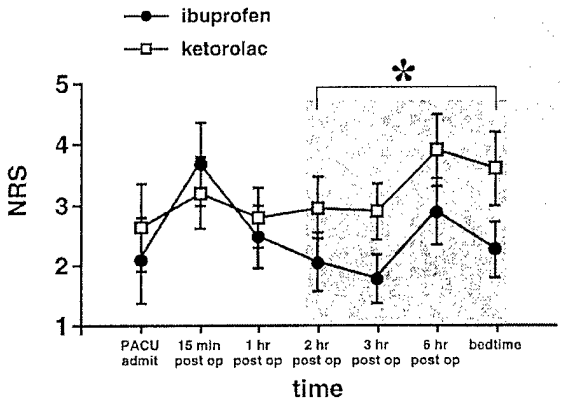


Figure 1.

orthogonal contrast of the first 3 periods (admission to PACU through 1 hour postoperatively). While there was no difference between groups in the NRS scores during the first one hour postoperatively, the ibuprofen group had lower NRS scores ($p< 0.01$) than the ketorolac group over the period of two hours postoperatively through bedtime (C. Uyehara, personal communication July 31, 2000; see Figure 1.).

Demographic variables, which included age, ethnicity, ASA category, and BMI were calculated to quantify the sample characteristics using descriptive statistics. While there were no statistically significant results found between the two groups, there were three variables that *approached* significance; LMP, ASA category, and nausea experienced while in the hospital. The probabilities respectively were 0.053, 0.064, and 0.065. The level of significance determined by convention for this study was $p\leq 0.05$.

Further data analysis revealed a serendipitous finding while evaluating potential correlations between NRS scores and the various demographic variables. Additional data was obtained from a take-home questionnaire and/or follow-up telephone call survey. Forty-three of the 44 (97.7%) subjects either returned the take-home questionnaire and/or were contacted telephonically. A Pearson's Correlation test used to analyze the data revealed that Caucasian patients had significantly more nausea at home than Non-Caucasians ($p<0.01$).

As previously mentioned, study participants were asked to complete a take-home questionnaire. Thirty-two subjects (73%) completed and returned their questionnaires. Of the12 who did not return their questionnaires, six were from Group I and six were from

Group II. The study participants were asked to rate their pain six hours after surgery, at bedtime, and indicate the location of their pain (Table 5).

Table 5

Location of Participants' Pain

Pain location	Group I (n=17)	Group II (n=15)
Six hours after surgery		
Abdominal pain	6	10
Abdominal and back pain	1	0
Abdominal and throat pain	1	1
Abdominal pain with cramps to knees	1	1
"Cramps" with no area specified	1	0
Upper thigh pain	1	0
Low back pain	1	0
Incisional pain	4	2
No pain	1	1
Total	17	15
Bedtime		
Abdominal pain	5	10
Cramps from abdomen to knees	1	0
Abdominal and throat pain	1	1
Abdominal and chest pain	0	1
Low back pain	1	0
Incisional pain	5	3

No pain	4	0
Total	17	15

Both groups at six hours after surgery had primarily complaints of abdominal pain (total = 16). Many subjects indicated they had abdominal pain plus pain at another site (total = 21). When combining abdominal pain with other types of pain, nine from Group I and 12 from Group II had abdominal pain. Four from Group I and two from Group II complained of incisional pain. Group I had one subject complain of low back pain, one with cramps, and one with pain in the upper thighs. Both groups had one subject each that reported no pain at six hours after surgery.

Again, both groups at bedtime primarily had complaints of abdominal pain. When combining abdominal pain with other types of pain, seven from Group I and 12 from Group II had abdominal pain. Five from Group I and three from Group II complained of incisional pain. Group I had a single subject with low back pain. Four subjects, all in the ibuprofen group, reported having no pain at bedtime.

Participants were asked if they used any other methods to relieve their pain after surgery to include prayer, heat/cold packs, position in bed, meditation, etc. Twelve subjects reported they used no other methods to control pain, one used prayer, six used hot/cold packs, 17 used position in bed, and several used more than one method to relieve pain.

The following four questions regarding the participants' overall feelings toward surgery/anesthesia services were asked: (a) How was your surgical experience? (b) Was there anything that we could have done differently? (c) How was your overall satisfaction

with pain control? (d) What was it like to be in this study? Overall and regardless of group assignment, the participants had positive comments.

Twenty-two participants were satisfied or very satisfied with their surgical experience, three do not remember their surgical experience, two were dissatisfied with the waiting time, and five voiced various other concerns (tape removal, sore throat, pain, and nausea). Direct quotations from the participants' answers to the first question, " How was your surgical experience?" include the following:

> "It was fascinating to me after I was awake. I did not know nothing [sic] just like the doctor and anesthesia personnel told me."
>
> "Fine except I waited an hour in that cold room after my name was called."
>
> "Good. Postop was painful at first, but I was taken good care of."
>
> "Personal quite pleasant. Doctors, nurse, everyone was very nice and helpful. I did not experience any pain so far from this surgery."

Of the 31 study participants who responded to the question about what could have been done differently, 21 subjects felt that nothing needed to be changed. Five of the ten participants that wanted something changed, voiced dissatisfaction with the amount of time spent waiting. The other five women wanted changes ranging from better preoperative counseling, to giving less amounts of anesthesia, and not relying on the chaperones to relay discharge instructions. (Note: In addition to the verbal information provided to the patient and their escort, written instructions with a phone number in case of any questions, are also given to the patient upon discharge from the hospital). Direct quotations from the participants' answers to the second question, "Was there anything we could have done differently?" include the following:

> "You have done [an]excellent job. I [am] so proud of you [sic] all personnel that [were] involved with my surgery. Thank you."

"Explained and stressed that the patient would have been there all day. I arrived at 8:40 am and finally left at 6:00 pm. I had no idea I would be there all day."

"Maybe less anesthesia. I've had 3 previous surgeries and never felt this bad with nausea."

"I'm pleased with everything."

Twenty-five of the thirty-two participants, who returned their questionnaires, were satisfied with their postoperative pain control, but 2 of the 25 were satisfied only after receiving additional pain medication. Four of the five subjects who were not satisfied with their postoperative pain control were from Group II (ketorolac group). Two women out of the thirty-two did not state whether they were satisfied or not, but one of them did say she was having pain upon awakening from anesthesia. Direct quotations from the participants' answers to the third question, "How was your overall satisfaction with pain control?" include the following:

"Excellent. Excellent. A++."

"Satisfied with what was done to manage pain."

"Not satisfied. Although there was no pain at the incision sites or internally, the lower back pain was surprising, and unrelieved by the pain medication until almost 7 hours after surgery."

"Very satisfied once I got enough morphine."

When asked what it was like to be in the study, 19 participants expressed positive aspects ranging from exciting to "no problem." Nine of the nineteen subjects felt it was exciting, interesting, or a pleasure to be invited to participate; four felt it was "nice to be helpful;" and six felt it was "ok" or "no problem." Seven subjects stated that there was little or no difference by participating in the study. Four subjects noticed a difference, but did not state whether it had positive or negative impact. When asked if they would like a copy of the study results, 26 subjects wanted a copy, five did not want a copy, and one

did not answer the question. Direct quotations from the participants' answers to question four, "What was it like to be in this study?" include the follow:

> "It's a new challenge to me. I would recommend to all [who have] surgery, [that they] should do what I did. I feel special that I have been part of your study. I [hope] you all [have] good result from you [sic] study on me."
>
> "No different than any other surgical experience."
>
> "I was happy to help."
>
> "I had no real expectations or thought on the matter really."
>
> "Glad to be a part of the medical system. Especially if it is helping others in the future."

Summary

There was no significant difference in the total dosage of intravenous rescue medication for postoperative pain and elapsed time until the first dose of rescue medication (either intravenous in the hospital or orally at home). However, two statistically significant differences were found following analysis of the data. First, patients who received ibuprofen 800 mg orally before surgery had significantly less pain from two hours postoperatively until bedtime ($p<0.01$). Second, eighty-two percent of Caucasian patients reported nausea at home, which was significantly more than Non-Caucasian patients ($p<0.01$).

As previously discussed in Chapter III, a desired sample size of 20 subjects per group was used based on a post hoc power analysis of the study by Higgens et al. using Sample Power v1.2 (SPSS, Inc.). The main effect of drug differences seen between ketorolac and ibuprofen yielded a medium effect size of 0.25 and a power of greater than 0.80 when using 20 subjects per group. Our study treated the NRS as interval level data, therefore validating our post hoc power analysis of the study by Higgins et al. (1994)

which used parametric statistics to analyze VAS scores. A total "N" of 50 was used to allow for subject attrition.

The final sample size was 44, with a resultant subject attrition of 12.0%. Six subjects who participated in the study were excluded for the following reasons: (a) Three patients had additional surgery performed; (b) one patient had a history of acute pain; (c) one patient received only one gel caplet instead of four, resulting in a protocol violation; and (d) one patient had a preoperative urine Hcg returned as positive on the morning of surgery. Our final power derived from an "N" of 44 was greater than 0.80 in order to detect a medium effect size of $\geq$0.25. Thusly, the possibility of a Type II error would be considered minimal.

CHAPTER V

Discussion, Conclusions, Implications, and Recommendations

Voluntary sterilization is the most commonly used method of contraception worldwide with over 10 million women in the U.S. alone electing surgical sterilization each year (Gentile et al., 1998; Napalitano et al., 1996). ILBTS is the most common surgical procedure for female sterilization, and is routinely performed on an outpatient basis despite reported variation and problems with post-laparoscopy pain (Cade & Kakulas, 1995). This became the impetus for this study, as anesthesia providers remain challenged to facilitate timely discharges while consistently managing postoperative pain following this surgical procedure. The current body of related literature has revealed a contemporary method of decreasing postoperative pain using preemptive analgesia, of which there are several modalities.

Preemptive analgesia follows the premise that it is easier to prevent pain rather than titrate medications to reduce pain once it has already been established (Agency for Health Care Policy and Research, 1997). Preemptive analgesia is based on the pharmacodynamic effects that specific drugs have on the central and peripheral mechanisms in the pain pathway that follow tissue injury. Central nervous system modulation of pain involves the wind-up and sensitization of second-order neurons, which results in the continued volley of afferent pain impulses to the brain even after the peripheral stimulus has ceased. The peripheral mechanism of pain modulation involves the heightened sensitization of nociceptors (peripheral pain receptors) which transmit noxious stimuli following the inflammatory process with tissue injury. Both of the

aforementioned involve the production and release of prostaglandins (one of several pain producing substances known as an alogens) via the arachidonic acid cascade. NSAIDs inhibit the enzyme cyclooxygenase, and thus the production of prostaglandins through this cascade. Preemptive analgesia is based on prevention of the heightened nociceptive state. Therefore, it is theorized that by administering NSAIDs before surgical trauma, the chemical mediators of inflammation and modulation will be inhibited, which in turn decreases the inflammatory response peripherally and wind-up of second order neurons centrally, thus reducing the resultant pain. Decreased postoperative pain would reduce the untoward physiological and psychological effects, improve patient outcomes, and lessen the economical effects stemming from unplanned hospital admissions.

The results from previous studies have varied when using ibuprofen and ketorolac preemptively in this surgical population. Factors that remain to be considered include clinical efficaciousness, cost containment, and overall patient satisfaction. The goal of this study was to compare postoperative pain among ILBTS patients when given one of these two NSAIDs before surgery. This chapter will begin with a discussion of the research findings, followed by pertinent conclusions, implications for practice, and recommendations for future research.

Discussion

The hypothesis stated that in patients undergoing ILBTS who preemptively receive either ketorolac 30 mg intravenously or ibuprofen 800 mg orally, there will be a difference in (1) the amount of postoperative pain, (2) the amount of opioid administered postoperatively, and (3) the elapsed time until the first rescue medication is given. Study

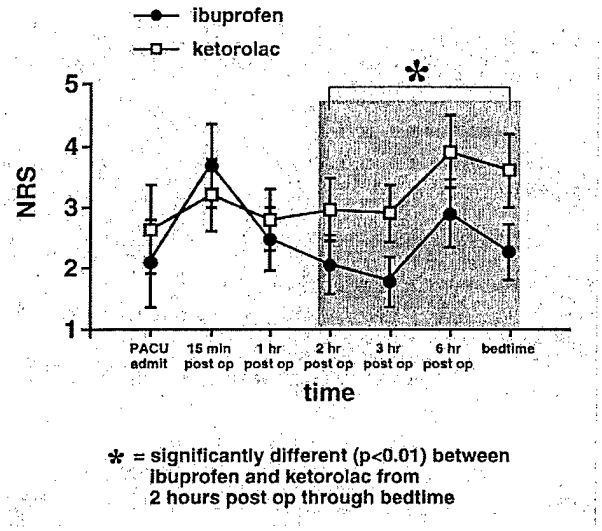
findings supported partial rejection of the null hypothesis: There will be no difference in the amount of reported postoperative pain. When the mean postoperative pain scores were analyzed over time, a statistically significant difference was observed; the group that received ibuprofen orally had lower postoperative pain scores than the group that received ketorolac IV ($p<0.01$). An additional finding of statistical significance was that Caucasian patients reported more nausea at home than African-American or Hawaiian/Pacific Islander patients ($p<0.01$).

Relationship of Findings to Role Studies

Postoperative pain is the undesirable sequela that follows the residual anesthetic provided for a surgical procedure. However, in recent years with an improved understanding of pain physiology, preemptive analgesia has received increased attention, with several pharmacologic modalities having been tested. NSAIDs have been shown to inhibit the release of chemical mediators of pain and inflammation following tissue trauma. They have a proven opioid-sparing effect, and while the existing body of literature has some varied results, most of the findings support the preemptive administration of NSAIDs.

Data analysis revealed statistically significant findings with regard to postoperative pain scores when measured by the patients using the NRS. Patients who before surgery received ibuprofen 800 mg orally had lower overall pain from 2 hours after surgery until bedtime when compared to patients who received ketorolac 30 mg IV before surgery (Figure 1). In addition, the bimodal data has predictive value. As seen in Figure 1, patients in both groups had an initial increase in pain scores at 15 minutes

Figure 1.



following the end of surgery. However, there was a direct correlation between the second and sixth NRS scores. The functional relevance of this aspect will be discussed later in the chapter. Our results contrast those in the study by Higgens et al. (1994) which showed no significant differences in pain scores between the control and experimental groups. We designed our study in order to minimize what we perceived as possible extraneous variables in the Higgins et al. study, and included the following: (a) allowing time for the preemptive medications to peak before surgical incision; (b) standardizing the anesthetic which included excluding succinylcholine (postoperative myalgias have been attributed to fasciculations) and adjusting fentanyl dose to a maximum of 5 mcg/kg; (c) no oral gastric tube (in order to not remove any remaining oral drug, therefore, affecting the outcome of the study); (d) initiating a more aggressing protocol for rescue medications for postoperative pain; and (e) a post hoc power analysis indicated the Higgins et al. study needed at least 20 subjects per group.

Theoretical Framework Used to Guide Research

The theoretical framework for this study used a physiological model depicting central and peripheral mechanisms that have been studied in the pain pathway. In addition, a pharmacological model provided a viable approach to preemptively mediating pain that is transmitted via the aforementioned pathways by inhibition of the enzyme cyclooxygenase. As previously discussed, NSAIDs' inhibition of this enzyme halts the production of prostaglandins, which heightens the nociceptive state in the periphery and leads to the production of excitatory amino acids in the central nervous system. By blocking the ability to produce prostaglandins in the body, postoperative pain following tissue trauma is decreased.

We elected to also have 0.5% bupivicaine drops applied to the tubes of the patients in both groups. Based on the current body of knowledge in the literature that includes the studies by Guard & Wiltshire (1996), Kelley et al. (1994), and Van EE et al. (1996), it is apparent there is presently no one single drug/modality that can appreciably preempt postoperative pain. A balanced or multimodal preemptive analgesia regimen appears to be the most pragmatic contemporary approach (Alexander, 1997; Chung et al., 1997; Kelly et al., 1995; & Wittels et al., 1998).

We felt that the current body of literature supports the premise for preemptive analgesia (Cabell, 2000; Dahl & Kehlet, 1993; Garrett & Mc Shane, 1999; Goodwin,1998; & Woolf & Chong, 1993). Therefore, we believed that the use of a control group for this study could be construed as unethical by withholding treatment that would be expected to benefit the patient.

Our data analysis revealed an initial increase in postoperative pain scores in *both* groups at 15 minutes after the end of surgery. We feel this could be attributed to the clinical analgesic effect of fentanyl given intraoperatively had subsided (normal analgesic effect seen clinically is 0.5-1.0 hour when administered IV) and rescue IV morphine had either not been given or had time to peak if given in the early postoperative period. Furthermore, the patients were probably less sleepy and becoming more cognizant of any pain or discomfort they were experiencing. In addition, this was the only NRS score where ibuprofen was higher than ketorolac.

Our conjecture was formed following a serendipitous discovery during the data collection period. A study participant was being visited by one of the investigators in the SAC during her Phase II recovery period. The investigator noticed two partially dissolved tablets in a kidney basin at the patient's bedside (following emesis). This opened the possibility that the gel caplets that were used by the in-patient pharmacy to disguise the ibuprofen and placebo tablets were not absorbed into the gastrointestinal tract as readily as anticipated. Therefore, with regard to the aforementioned NRS score, we postulated that the group that received ibuprofen had a possible delay in absorption of the drug, and therefore a delay in onset and peak of the drug as well.

Both groups had a decrease in mean pain scores at 1 hour postoperatively. The ketorolac group maintained a relatively steady-state in reported pain scores through three hours postoperatively. Conversely, the ibuprofen group continued to show a steady decline in mean pain scores through the third postoperative hour. At six hours postoperatively, both groups showed a second increase in mean pain scores. This could

be secondary to: (a) the diminishing analgesic effects of the local anesthetic drops and NSAIDs given preemptively (half-life elimination time: ketorolac 2-8 hours and ibuprofen 2-4 hours), (b) the car ride home and household activities may have contributed to the patient's sensation of pain/discomfort, and (c) the patients may not have taken their prescription medication, or if taken, the therapeutic level had not been reached.

The demographic comparison between the two treatment groups showed a difference in reported elapsed days since last menstrual period that approached a level of significance (p=0.053). Group II patients had a mean of 23.7 days reported since their LMP; it would not be unreasonable to expect that this group could have experienced increased abdominal cramping/discomfort associated during the pre-menstrual period. This *could* explain, therefore, why the ketorolac group reported higher postoperative pain scores. Our conjecture is that the ketorolac group may have experienced an additive effect from cramping associated during the days preceding a woman's menses. However, subjects were not asked to discern beyond the location of their pain/discomfort; it would have been beneficial to have them further define or clarify in their own words what they were experiencing. It is possible that the discomfort they encountered postoperatively was incisional pain, deep pelvic pain, or a derivation of referred pain.

Similarly, a goal of our design was for both drugs to achieve peak effect at the time of direct laryngoscopy. We feel the ibuprofen group achieved this goal with a mean of 64.9 minutes from the time of administration until laryngoscopy. However, the mean was 16.3 minutes for the elapsed time from ketorolac administration until laryngoscopy (time to peak effect is 30-60 minutes per package insert). While the ketorolac group

reached peak levels by the time of surgical incision (mean elapsed time 45.0 minutes), it had not peaked at the time of direct laryngoscopy and tracheal intubation. Since some researchers have suggested that wind-up occurs as early as placement of a peripheral IV or with laryngoscopy (L. Dahl, personal communication, August 19, 1999), we propose this could have been a factor in Group II reporting higher NRS scores.

Analysis revealed that Caucasian patients had significantly more nausea at home than African-American or Hawaiian/Pacific Islander patients ($p<0.01$). A correlation analysis did not expose any relationships between nausea reported at home and any of the other demographic or anesthetic variables. As shown in Table 3, there were 14 Caucasian patients in each group. While Group II was actually closer to their menses at the time of surgery as reported earlier, we examined and found there was no difference between the two groups in nausea at home ($p=0.934$). Additionally, there was no difference in the amounts of intraoperative fentanyl or rescue morphine/demerol given postoperatively. Therefore, further study may be warranted as there are no obvious correlations from our study or findings reported in the current literature.

Analysis of data obtained from the take-home questionnaire revealed information that enriches the quantitative findings of this study. Also, some of the comments, gleaned from the participants, impact clinical practice. Finally, analysis of the home questionnaire data stimulates many questions that warrant future research.

One interesting finding of the take-home questionnaire was that the duration and type of pain experienced by the women in our study differed from what is reported in the literature. Four types of pain after laparoscopic sterilization have been reported.

Subphrenic/shoulder pain is the first type of pain, and may persist until the third to fourth postoperative day (Alexander, 1997; Dobbs et al., 1987; Goldstein et al., 2000; Guard & Wiltshire, 1996). None of the patients in our study complained of this type of pain. Deep pelvic pain is the second type of pain, and rarely lasts for more than six hours postoperatively (Alexander, 1997; Chi & Cole, 1979; Davis & Miller, 1988; Dobbs et al., 1987; Goldstein, 2000; Pelland, 1987). Spasmodic/cramping pain is the third type of pain, and hardly ever lasts longer than three to four hours (Dobbs et al., 1987: Edwards et al., 1991; Guard & Wiltshire, 1996). In our study we combined deep pelvic and spasmodic/cramping pain into the category of abdominal pain. In the literature this pain has been reported to usually last no more than six hours. Our take-home questionnaire revealed that 22 subjects (six hours after surgery), and 19 subjects (at bedtime) reported abdominal pain. Incisional pain is the fourth type of pain, and has been regarded as being incidental by other researchers. (Cade & Kakulas, 1995; Rasanayagam & Harrison, 1996; White, 1997). Six participants responded on the home questionnaire with complaints of incisional pain six hours after surgery, and eight had this type of pain at bedtime.

While our take-home questionnaire inquired as to where the subject's pain was located, we did not have them provide details regarding the type of pain. A future descriptive study could be designed to discern whether subjects are indeed experiencing incisional pain, or actually having deep pelvic or spasmodic type of pain.

Conclusions

The following conclusions were attained following analysis of the data. Statistical analysis exhibited a significant difference in postoperative NRS scores between the two

treatment groups. While there was no difference in the amount of postoperative rescue medication or elapsed time until its administration, the patients who received ibuprofen preemptively had lower pain scores from 2 hours after surgery until bedtime when compared to the patients who received ketorolac preemptively. In addition, a serendipitous discovery unveiled that Caucasian patients had more nausea at home than African-American or Hawaiian/Pacific Islander patients. Of noteworthy importance is there were no patients from either treatment group with an unplanned admission secondary to retractable postoperative nausea and vomiting. This was of theoretical concern to us due to the introduction of a medication (ibuprofen) with the potential for gastrointestinal upset based on clinical reports.

Clinical Implications

In the facility where the study was conducted, the unit dose cost for an ibuprofen 800 mg tablet and ketorolac 30 mg Tubex® syringe is $0.02 and $5.24, respectively. In keeping with the contemporary focus of cost-containment, preemptively medicating this surgical population with ibuprofen 800 mg orally should be considered a cost-effective method of limiting postoperative pain while simultaneously minimizing the cost to the treatment facility. Several discoveries were made when comparing the data collection records with information gleaned from telephonic postoperative follow-up. Of particular interest was related to nursing documentation and implementation of nursing care.

We noted that several patients were transferred from the PACU (5 of 44) or discharged home from the hospital (7 of 44) with NRS scores of "5" or higher. However, there was no documentation as to whether this level of reported pain was either

manageable or tolerable by the patient. We submit there may be several plausible explanations. One may be related to the patients' understanding of the discharge protocol. That is, they may have requested to be released and subsequently reported that a rating of "5" was in fact manageable in order to be discharged home. Perhaps they wanted to leave as soon as possible in an effort to complete their convalescence at home. Moreover, their *perception* of the pain postoperatively may have been less than their *expectation*.

We also learned that a patient was given IV ketorolac in the SAC; this was not documented on the data collection record but was discovered on the postoperative record during a final chart review by the investigators. There was no physician/computer-generated order on record, and we were unable to find any written documentation of a physician's order for the medication. We suspect that in all reality, a verbal order was given without having been documented or entered in the computer. However, we are uncertain as to why an additional NSAID was administered (as patient folders and perioperative forms were clearly marked indicating the patient was in the study).

Similarly, several patients reported having nausea on the take-home questionnaire while in the hospital; however, this was not documented in either the nursing notes or in the data collection record use for the study. A form used by the ASC nursing staff *combines* nausea and vomiting with regard to patient status upon discharge home. Perhaps the aforementioned should be documented separately, which may foster additional focus on nausea. Moreover, a nursing note could reflect that nausea experienced is tolerable/manageable, or simply that the patient *desires* to be released so they may continue recovering at home.

We also noted that several patients reported a different NRS score for the 6 hour postoperative and bedtime scores when we followed-up telephonically the day after surgery. When this occurred, the NRS score reflected on the take-home questionnaire was always higher than what was reported during the telephone follow-up interview. This could be due to the scores recorded on the questionnaire were closer to the time when the pain/discomfort was experienced by the subject. Another conjecture is that when queried telephonically, the subjects may have felt compelled to respond in order to please the investigators (known as demand characteristics), as noted by Orne (1962). For the purpose of data analysis, we used the NRS score from the take-home data questionnaire (provided to the patient) if it was returned to the investigators. Otherwise, the reported verbal NRS score was utilized.

During the pilot study, we learned that several of the PACU nursing staff had a preference for administering meperidine versus morphine for postoperative pain; thus, they would contact a department anesthesiologist for a written order. We found this interesting as the investigators prior to initiating data collection reviewed the standardized PACU protocol. Additionally, there was no mention of the aforementioned during a formal in-service to the PACU staff provided by the investigators. Following the pilot, we met with the PACU staff and learned that they felt meperidine had some desirable euphoric qualities as opposed to morphine. We wondered how this perception may have evolved; moreover, why would euphoria be perceived as beneficial when discharge from the PACU in a timely manner is a relative priority. Perhaps this is an area that merits further investigation. Following the pilot study, however, it was mandated that

during the data collection period all subjects would receive morphine for postoperative pain in order to maintain homogeneity between the treatment groups.

During the course of the data collection period, several patients were not included in the study as previously described. Interestingly, the OB/GYN surgeons continued to apply 0.5% bupivicaine local anesthetic to the tubes along with requesting ketorolac 30 mg IV to be administered perioperatively to those women who were not in the study. The chief resident also indicated a strong interest in performing a follow-on investigation once our study was completed.

Of final importance to note is the following. There were several comments on the take-home questionnaire that addressed concerns about delays in proceeding to the operating room. Suggestions from the women included informing patients about possible delays preoperatively, and then keeping them updated when delays occur. Reminding staff to keep patients informed has immediate clinical implications that can significantly affect perceptions of the surgical experience.

Recommendations

Postoperative pain control in this surgical population continues to present as an anesthetic challenge. Anesthesia providers are continually seeking a pharmacologic modality that is both cost-effective and clinically efficacious. While both drugs used in the study are of the same class, we found it interesting that the drug proven to be effective in treating dysmenorrhea pain yielded better patient outcomes in this study. Therefore, we feel that the results of this study support the use of ibuprofen at several key time points, and are as follows.

We would recommend administering the drug before surgery at an appropriate interval that would allow for adequate onset/peak effect prior to surgical incision. Also as previously stated, the bimodal data revealed a correlation between NRS scores at 15 minutes and 6 hours after the end of surgery. The clinical importance is that it allows the anesthesia provider and nursing staff to educate the patient with the following in mind. The results show that if a patient had a hypothetical NRS score of "5" 15 minutes after the end of surgery, the patient could expect to have a similar level of postoperative pain at 6 hours following the end of surgery. If this was perceived as unmanageable or uncomfortable by the patient, then discharge teaching should include taking medications regularly up through bedtime to preempt postoperative pain that will predictably ensue.

Research Implications

This study was conducted in a military treatment facility (and teaching hospital) where the study participants were either active duty service members or dependents of active duty service members. Generalizations are only applicable to similar populations. Therefore, we would recommend a repeat of this study in a non-military/non-teaching facility, where a similar effect would hopefully be verified.

A possible follow-on study could involve two groups with the following design. Of two treatment groups, only one of the groups would take ibuprofen the night before surgery (in addition to a preoperative dose) in order to lengthen the preemptive effect of halting prostaglandin production.

Ibuprofen produced significantly better results in this surgical population. A similar study in other surgical populations is warranted whereby similar preemptive effects may be demonstrated.

A serendipitous finding revealed Caucasian patients had more nausea at home when compared to Non-Caucasian patients. A review of the literature was conducted following analysis that included the specialties of anesthesia and oncology; presently there is no data that reveals a relationship between PONV and ethnicity. Therefore, further investigation may be warranted.

Finally, information gleaned from the take-home questionnaire stimulates at least two prospective ideas for further study. The first would be to examine what motivates subjects to participate in research studies. Nineteen of the 32 patients who returned their home questionnaires expressed very positive aspects in participating in our study. The second would be to explore not only the location of pain following laparoscopic tubal sterilization, but to also express the type of pain the patients are experiencing.

Summary

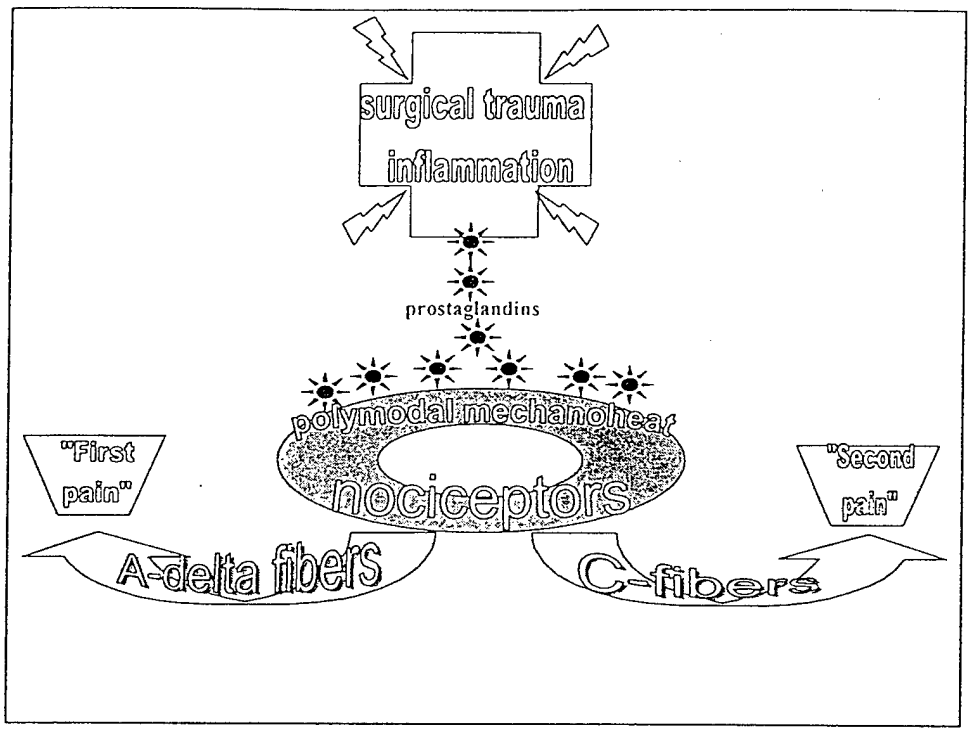
This prospective, double-blind, randomized study examined the effects on postoperative pain when ASA I/II female patients presenting for laparoscopic tubal sterilization were given either ketorolac 30 mg intravenously or ibuprofen 800 mg orally before surgery. Group I (received ibuprofen) consisted of 23 participants while Group II (ketorolac) had 21. There was a significant difference in reported postoperative pain from 2 hours after the completion of surgery until bedtime ($p<0.01$). A post hoc power analysis

of a previous study allowed for a power of >0.80 with at least 20 subjects per group. Therefore, the possibility of a Type II error should be minimal.

While the ibuprofen group reported more nausea postoperatively (p=0.064), there was no difference between the two groups in the antiemetics administered (p=0.339). In addition, no patient from either group was admitted for retractable PONV. The study was conducted in a military facility/teaching hospital; therefore, a follow-on study would be warranted to determine if similar results would be obtained in a civilian/non-teaching facility. Finally, a secondary analysis of the data revealed that Caucasian patients reported more nausea at home following discharge when compared to African-American or Hawaiian/Pacific Islander patients. Currently there is nothing reported in the literature with regard to ethnicity and PONV; therefore, this finding could provide a stimulus for further research.

APPENDIX A

Theoretical Framework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prostaglandins
polymodal mechanoheat
nociceptors
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"Second pain"
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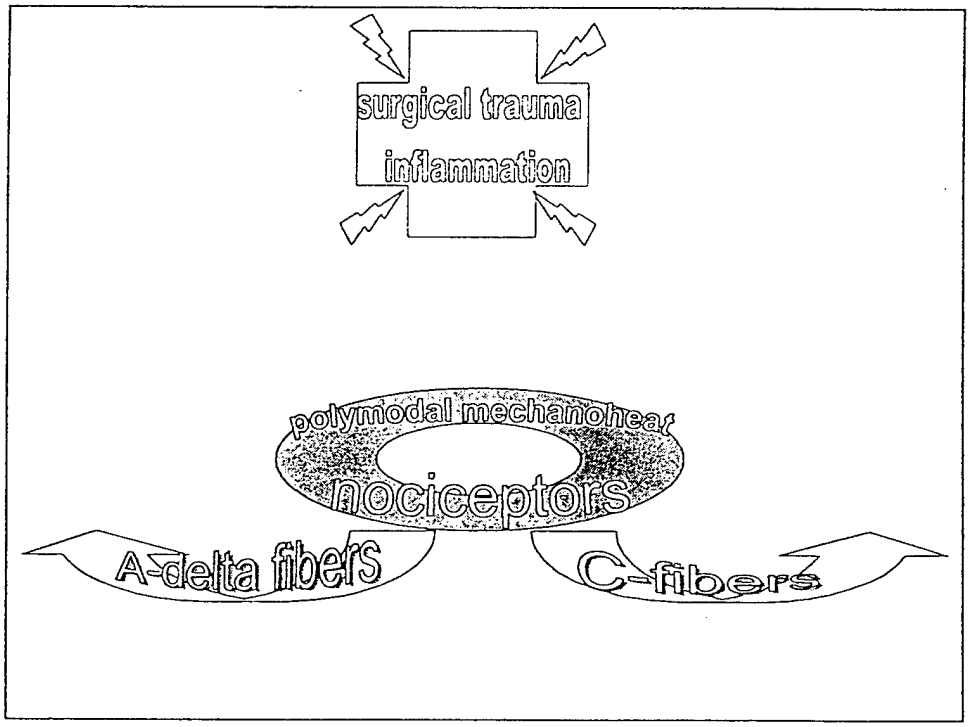
C-fibers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inflammation
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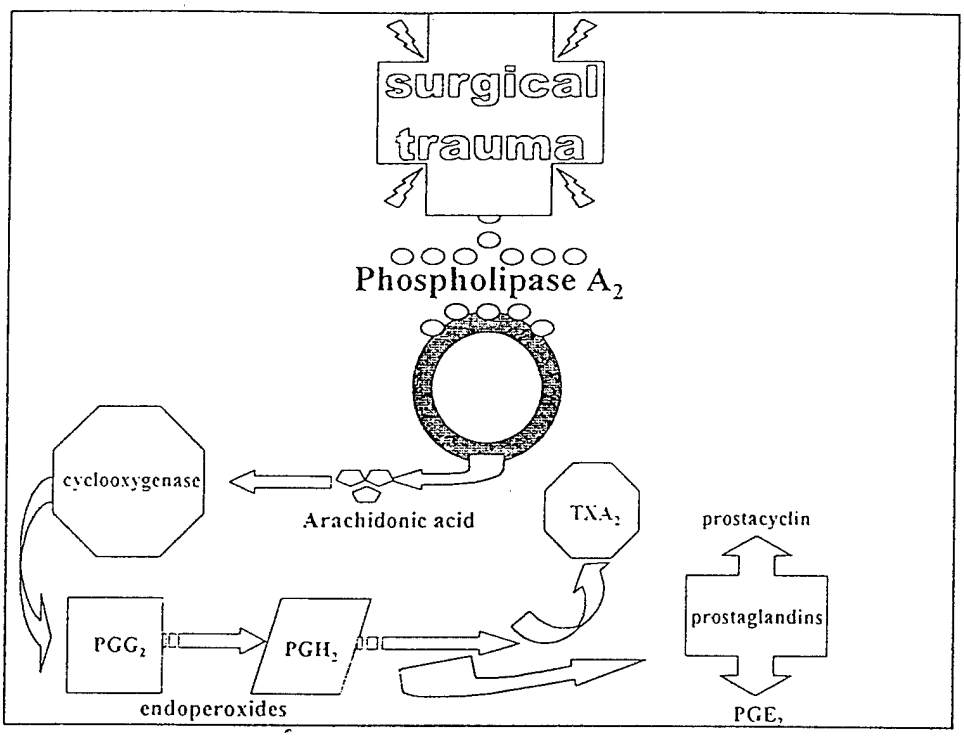
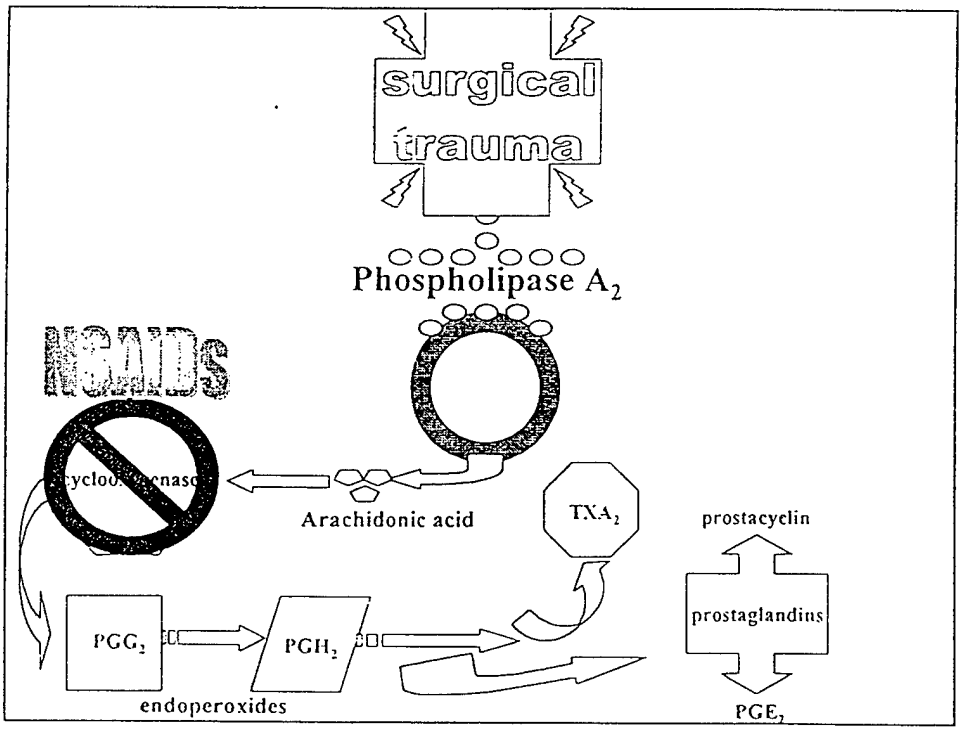
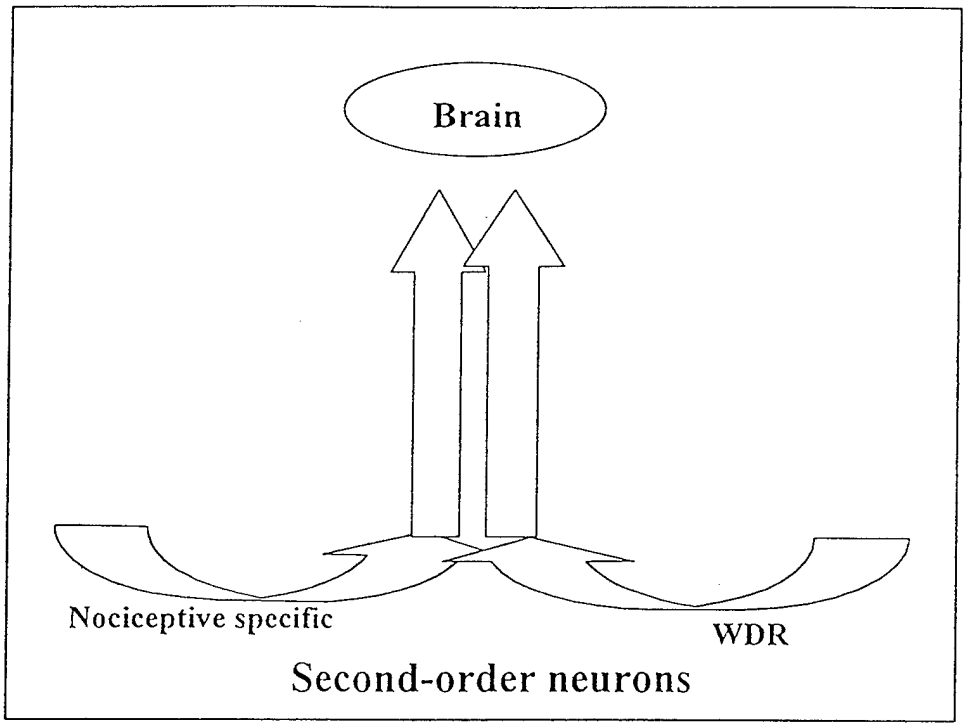

surgical trauma
Phospholipase A_2
cyclooxygenase
Arachidonic acid
TXA_2
prostacyclin
prostaglandins
PGG_2
PGH_2
endoperoxides
PGE_2


surgical trauma
Phospholipase A_2
NSAIDS
Arachidonic acid
TXA_2
prostacyclin
prostaglandins
PGG_2
PGH_2
endoperoxides
PGE_2


Brain
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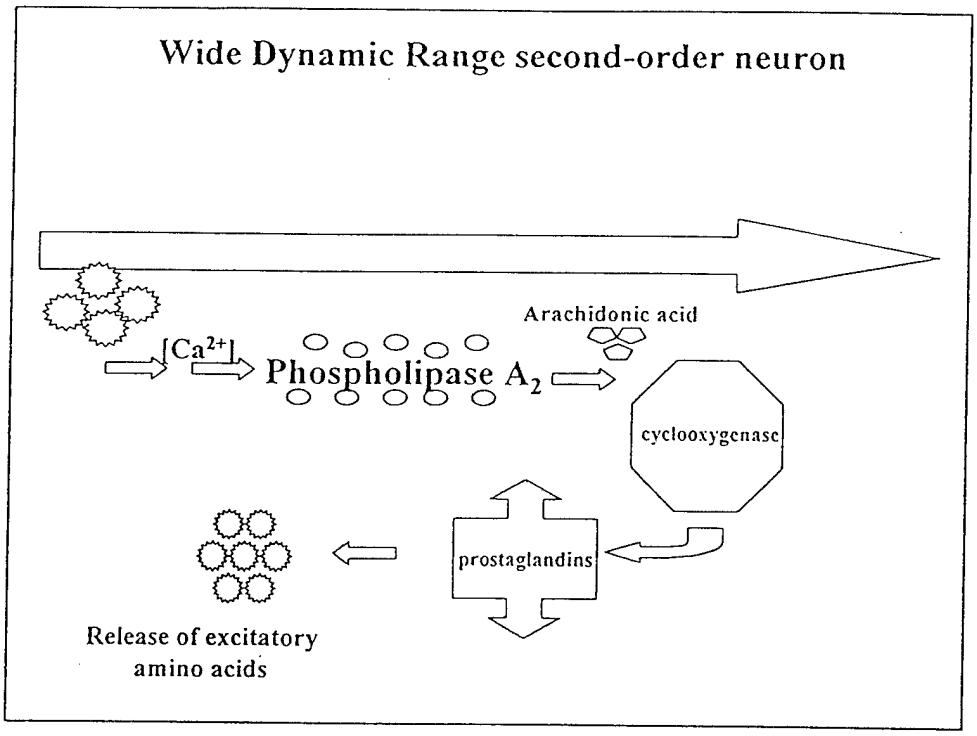
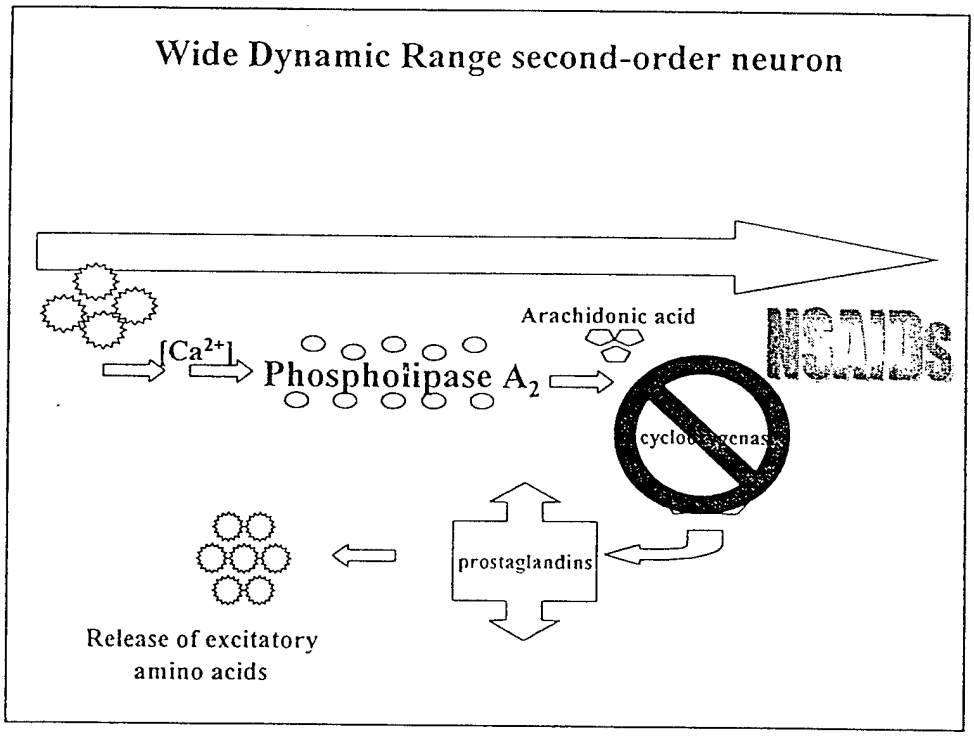
WDR
Second-order neurons


Wide Dynamic Range second-order neuron
Arachidonic acid
[Ca2+]
Phospholipase A2
cyclooxygenase
prostaglandins
Release of excitatory amino acids


Wide Dynamic Range second-order neuron
Arachidonic acid
NSAIDS
[Ca2+]
Phospholipase A2
prostaglandins
Release of excitatory amino acids

APPENDIX B

Exclusion Criteria Worksheet

Patient's Home Phone Number:_____

Exclusion Criteria Worksheet for Tubal Sterilization Study

Instruction: Please answer the questions below, if any are marked, the patient is **not** eligible for our study. Mahalo for helping us with our study.

- Please put a checkmark if the patient has any of the following **exclusion** criteria

_____ Does not understand English

_____ Less than 18 years old

_____ Weighs less than 110 pounds

_____ Allergic to NSAIDS or Aspirin

_____ Has asthma

_____ Has liver problems

_____ Has kidney problems

_____ Has bleeding ulcers

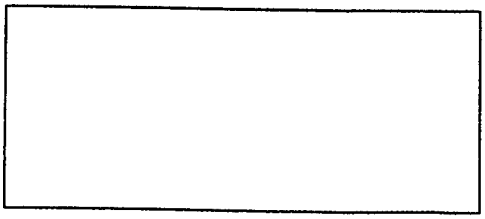
_____ Aspirin use within the last 10 days

_____ Psychiatric illness

_____ Less than six weeks postpartum on day of surgery

_____ Clinical indication for intubation requiring Succinylcholine

Patient ID



APPENDIX C

Data Collection Worksheet

Data Collection Worksheet

Preoperative Data

Patient ID #_____ Date of Surgery _____

Demographic/Preoperative Data

Age:_____Height:_____(cm)Weight:_____(kg) LMP _____

ASA Category:_____ Ethnicity _____

Numeric Rating Scale score: (to include location of pain)

Preoperative _____ Location _____

Time given oral ibuprofen/placebo: _____

Time given ketorolac/normal saline IV: _____

Intraoperative Data

Time of laryngoscopy _____

Time of first incision _____

Time when first fallopian tube occluded: _____ Type of tube occlusion _____

Duration of surgery _____ (min.)

Type/total narcotic given: _____

Anesthetics/Meds:

Midazolam_____(mg)

Fentanyl_____(mg)

Propofol_____(mg)

Rocuronium_____(mg)

Sevoflurane_____(%)

Glycopyrrolate_____(mg)

Neostigmine_____(mg)

Dolasetron _____(mg)

Other meds: _____

Postoperative Data

PACU arrival time: _____ discharge time: _____

Time to first administration of postoperative analgesic medication _____

Episodes of emesis: _____ Time(s): _____

Antiemetics received: Type _____ Amount _____ Time _____

Total dose & type of postoperative analgesic administration _____(mg)

Admitted? YES / NO If yes, where? _____ Why? _____

Numeric Rating Scale score & location of reported pain

_____immediately on arrival to the PACU

_____15 min. after arrival to PACU Location _____

_____1 hour postop, or discharge from PACU Location _____

_____2 hours postop Location _____

_____3 hours postop, or discharge from ASC Location _____

_____6 hours postop Location _____ Activity _____

_____at bedtime postop Location _____ Activity _____

Prescription pain medicines ordered on discharge: _____

Time of discharge from hospital _____

"Take home" questionnaire returned? YES / NO

APPENDIX D

Informed Consent

VOLUNTEER AGREEMENT AFFIDAVIT

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

PRIVACY ACT OF 1974

Authority:	10 USC 3013, 44 USC 3101, and 10 USC 1071-1087
Principle Purpose:	To document voluntary participation in the Clinical Investigation and Research Program SSN and home address will be used for identification and locating 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 _____

A Comparison of Postoperative Pain with Preemptive Administration of Intravenous Ketorolac versus Oral Ibuprofen in Patients Undergoing Interval Laparoscopic Bilateral Tubal Sterilization

(Research study)

under the direction of CPT Patricia S. Harm, AN

conducted at Tripler Army Medical Center, Tripler AMC, HI 96859-5000

(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 examination 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 _____

_____

(Research Study)

_____

under the direction of _____

conducted at _____

(Name of Institution)

(Continue on Reverse)

PART (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 other 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 examination 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

INSTRUCTRUCTIONS 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 research study conducted at Tripler Army Medical Center. It is very important that you read and understand the following general principles. (1) Your participation is entirely voluntary. (2) You may withdraw from participation in this study or any part of the study at any time. (3) Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. After you read this 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 having a bilateral tubal sterilization. The purpose of the study is to determine if the type of pain medication you receive before your operation makes a difference in the amount of pain you experience after your operation. We will be comparing two types of pain medications, both of which are commonly used to control pain. These medications are ibuprofen and ketorolac. Ibuprofen is an aspirin-like pill. Ketorolac is a liquid drug that is very much like ibuprofen. During this study, you will receive ibuprofen or ketorolac before your operation. No previously published studies have demonstrated clearly if one of these drugs will be more effective than the other in controlling pain after bilateral tubal sterilization.

EXPECTED DURATION OF SUBJECT'S PARTICIPATION: Your participation in this study will begin when you arrive in the Surgical Admission Center the day of your operation. Your participation in this study will end when you are contacted by phone the day after your operation, and after you return the home questionnaire. Therefore, your participation in the study will be for about six to eight hours while in the hospital. Additionally, you will receive a follow-up phone call at your home the day after your operation, and you will need to fill out a short questionnaire. The call will take about five to ten minutes of your time, and the questionnaire will take an additional five to ten minutes of your time.

WHAT WILL BE DONE: After agreeing to participate in this study, you will be randomly assigned into either a group that receives ibuprofen or a group that receives ketorolac. Random assignment is a process like flipping a coin, and means that you have about an equal chance of being assigned to either group. The drugs will be coded, so that neither you nor the individual providing your anesthesia will know which of the two groups you are in, or whether you are

receiving ibuprofen or ketorolac. Should your medical condition require it, we can break the study drug code for the two drugs, determine which drug you are receiving and provide any other treatment that is necessary.

When you arrive at the Ambulatory Surgical Center, you will be given four capsules to take by mouth (one hour before your operation). The four capsules will either contain 800 milligrams total of ibuprofen, or a placebo (a placebo is like a sugar pill, and has no medical effect).

When you are brought down to the area that you wait in just prior to going into the operating room, a intravenous line (a small plastic catheter) will be placed in one of your veins. Thirty minutes prior to your operation, either liquid ketorolac 30 milligrams or liquid placebo (normal salt water that has no medical effect) will be given in the intravenous line.

Before your operation, we will ask you to rate your pain on a scale of zero to ten, with zero being no pain and 10 being the worst pain possible. We will also ask you to describe the location of your pain. We will ask you to rate any pain you may be having, and its location, seven more times after this: (1) when you first get to the recovery room after your operation, (2) 15 minutes after you get to the recovery room, (3) one hour after your operation or when you are discharged from the recovery room, whichever comes first, (4) two hours after your operation, (5) three hours after your operation or discharge from the hospital, whichever comes first, (6) six hours after your operation, and (7) at bedtime the day of your operation.

You may request additional pain medication at any time during this study. Your participation in the study will not affect your ability to receive additional pain medications.

We will give you a short questionnaire to take home, to rate your pain and its location (six hours after your operation and at bedtime the day of your operation). This questionnaire includes a scale (a line that shows the zero to ten pain rating, with zero being no pain, and ten being the worst possible pain), like the previous ones you have done. It also asks about the location of your pain, and what type of activity you were doing when you recorded your pain. We will call you at home the day after your surgery, to ask how you are doing, and to ask about your last two pain rating scores. We will also give you a stamped, addressed envelope so you can return the questionnaire to us.

REASONABLY FORESEEABLE RISKS OR DISCOMFORTS The risks and benefits of bilateral tubal sterilization and anesthesia have been explained to you separately, and you have signed a separate consent for the operation. Ibuprofen and ketorolac are strong, aspirin-like drugs used for pain relief, and have potential side effects. They may cause bruising or bleeding at the surgical site, stomach ulcers, kidney dysfunction, or allergic reactions. An allergic reaction may create generalized swelling and sudden changes in heart rate and blood pressure. Before you were invited to participate in this study, we screened you carefully to ensure that you have no health problems that might make it more likely for you to have any of these side effects. Additionally, these side effects are very rare when you are receiving only one dose of these medications.

Also, we will be calling you at home the day after your surgery, and you may perceive this as a minor inconvenience.

COMPENSATION FOR INJURY: In the event of physical injury or illness resulting from the research procedure(s), medical treatment is available and compensation may be available. For information regarding legal aspects of participation, contact the Center Judge Advocate, at (808) 433-5311.

BENEFIT(S) TO THE SUBJECT OR TO OTHERS: There may be no benefit to you from participating in this study. One of the goals of anesthesia is to control pain, to include pain control during initial recovery from the operation. If either drug we are using for this study provides better pain relief than the other drug, you may have less or no pain following your operation. Good pain control should improve your satisfaction with your operation and the outcome of your operation. Additionally, using the best pain medication, and choosing the best method of controlling pain, may reduce the potential for complications from the medications or operation. This could mean that patients in the future might have less pain, have fewer complications, and be less likely to be readmitted to the hospital.

ALTERNATIVE PROCEDURES OR COURSES OF TREATMENT: You may choose not to participate in this study. If you choose not to participate, your anesthesia care (including pain medication) will be the standard of care for your procedure. This may include your receiving ibuprofen or ketorolac for pain control.

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 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 reported to appropriate medical or command authorities.

PRECAUTIONS TO BE OBSERVED BY SUBJECT BEFORE AND FOLLOWING THE STUDY: There are no precautions to follow that are specific to your participation in 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: **Approximately** 50 patients.

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,

Patricia S. Harm, CPT, SRNA
Department of Nursing/DOHET
(808) 433-2132

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.

_____ _____

Typed Name & Signature of Volunteer Date

_____ _____

Typed Name & Signature of Witness Date

APPENDIX E

Medication Order Set

Medication Ordering Procedure for Ketorolac –vs- Ibuprofen Study

(A Comparison of Postoperative Pain with Preemptive Administration of Intravenous Ketorolac versus Oral Ibuprofen in Patients Undergoing Interval Laparoscopic Bilateral Tubal Sterilization)

1. **Inpatient pharmacy will be notified of study kit orders telephonically at 3-5314 / 6337 by an investigator.**
   The nurse anesthetist resident will be responsible for entering the orders into CHCS using the drug **Ketorolac Study Drug IV** with the SIG **"Ketorolac IV versus Ibuprofen PO".**

2. **To order using the ORE menu:**
   The order will be an outpatient Rx order for **"Ketorolac Study Drug – IV..."**
   Use the pathway:
   → *ORE*
   →*Enter Patient's Name*
   → *Select* Requesting Location – **OR/RR**
   → *Select* Clinical Service / MEPRS Code - **DFCA**
   → *Action* - NEW
   → *Select Order Type* – **RX**
   →*Select Outpatient Medication* – **Ketorolac Study Drug**
   →*From the list pick* **Ketorolac Study Drug – IV 30mg/ml INJ KIT**
   →*SIG* – **Ketorolac IV versus Ibuprofen PO**
   →*QTY* – **1**
   →*Order Comment* – **Study Drug**

3. **The investigator or her representative will come to the Inpatient Pharmacy to pick up the kit(s).** Kits will be picked up on the following morning no later than 0700hrs.

APPENDIX F

Post Anesthesia Care Unit Admission and Transfer Criteria

TRIPLER ARMY MEDICAL CENTER
POST ANESTHESIA CARE UNIT
TRIPLER AMC, HI 96859-5000
PACU SOP B-3

29 JUN 99

ADMISSION and TRANSFER CRITERIA

I. **PURPOSE:** To establish the policy and criteria for acute post surgical patient admission into the Post Anesthesia Care Unit (PACU) for intensive observation, assessment, evaluation, and quality health care, and to institute criteria for transfer of these patients.

II. **RESPONSIBILITY:** The Head Nurse will enforce the guidelines established by the Chief, Anesthesiology and Chief, Anesthesia Nursing.

III. **SCOPE:** This policy applies to all personnel assigned to work in the PACU.

IV. **POLICY:**

A. All the admission and transfer management policies and procedures are established through the interdisciplinary collaboration between the Head Nurse, Chief, Anesthesiology and Chief, Anesthesia Nursing.

B. Admission Criteria into the PACU:

1. All patients as determined by a Tripler staff anesthesiologist or CRNA who require intensive observation, assessment, evaluation, and health care for a short period of time following an operative or medical procedure for which an anesthetic agent was employed.

2. Patients who have received general anesthesia, regional anesthesia, local anesthesia, and / or intravenous (IV) sedation and analgesia who require Phase I recovery observation and care.

3. The PACU hours of operation are Monday through Friday, 0645-1830 hours and closed on the weekend days, military holidays and training days. Patients requiring Phase I recovery after 1730 hours will be recovered in an available room in the Critical Care section after consulting with the Department of Nursing Evening / Night Supervisor.

C. Transfer / Discharge Criteria from the PACU:

1. This PACU uses the Post Anesthesia Recovery Score (PARS) system (scale of 0 to 10) as one of the objective measurement criteria of a patient's protective reflexes, physical condition, and mental alertness. The PARS will be documented on

This supersedes "Admission and Discharge Criteria for Post Anesthesia Care Unit (PACU)" dated 1 SEP 98.

PACU SOP B-3 ADMISSION and TRANSFER CRITERIA

FORM DA 4700, TAMC OP 206-2, TAMC Post Anesthesia Care Assessment and Planning sheet.

2. A patient can be transferred from the PACU if specific criteria have been met, concise, accurate documentation is complete, there is reserved space ready to receive the patient, the receiving nurse has received a telephonic report, and the professional opinion concurs with the transfer. Generally a physician's presence or signature for release is not required at the time of transfer.

3. The transfer of a patient from the PACU is commenced when the following conditions are met:

   a. a PARS of eight (8) or greater.
   b. the patient's pain level is a three (3) or less on a 0-10 scale, or reports pain as tolerable.
   c. the patient does not have a sensation of immediate nausea or vomiting.
   d. the patient's bladder is not distended.
   e. patients with regional anesthesia will have progression of normal sensation two dermatone levels inferior to the admission level, while patients going to the ward will be at a dermatone level of L-1 prior to transfer.

4. If the transfer criteria can not be met, or there is a professional question at issue, the anesthesiologist on-call will be consulted. He / she will be designated as the PACU physician of the day. This will be the contact person for any questions or problems related to post operative management or health care of patients in the PACU. He / she can authorize transfer but must sign the release found on the front page of FORM DA 4700, TAMC OP 206-2, TAMC Post Anesthesia Care Assessment and Planning sheet.

5. The patient must be clinically stable and must meet the following PARS transfer criteria:

   a. Consciousness: Unless otherwise indicated by medical history or recent surgical procedure the patient is:

      1. awake and alert, or easily awakened.
      2. oriented to person, place, and time.
      3. capable of calling for assistance.

   b. Color: Unless prior state of health dictates, the overall skin color is considered normal for the patient.

   c. Circulation: The vital signs, hemorrhage, and urine output are considered in the following:

PACU SOP B-3 ADMISSION and TRANSFER CRITERIA

1. stable Blood Pressure (BP) and heart rate.
2. heart rate within +/- 20% and cardiac rhythm as documented per pre-operative.
3. BP within +/- 20% of patient's considered normal values.
4. tympanic temperature 96 - 100.4 F (unless baseline status was elevated pre-operative).
5. no evidence of hemorrhage, complications have been reported to surgeon and corrections have been made.
6. urine output via foley catheter is a minimal 30 ml/hr or 0.5 ml/kg/hr, (unless the patient has prior renal medical history).

d. Respiration: The following conditions must be met:

1. patient able to breath deeply and cough on command.
2. respiratory rate within normal limits for age.
3. no evidence of cyanosis or respiratory depression.
4. oxygen saturation via pulse oximeter is greater than 95% on room air, unless the patient has a medical history of respiratory ailment.
5. any chest x-ray taken in PACU must be read by a physician and a clearance given before a patient can be transferred.

e. Activity: Unless otherwise indicated by medical history or recent surgery, the patient can:

1. move all extremities.
2. lift head off gurney and hold for five (5) seconds.
3. turn on command.
4. patients with regional anesthesia may be transferred without the complete return of muscle movement or sensation if all other criteria are met and the operative site is free from complications.

6. The drainage tubes and catheters will be patent and functioning properly. Excessive and / or abnormal drainage has been reported to the surgeon and documented on the flow sheet. There is no evidence of bladder distention or excessive urinary retention prior to transfer.

7. Avoiding complications of anesthesia:

a. if an IV analgesic, IV anti-emetic, and / or initial antibiotic medication is given the patient will remain in the PACU for an additional fifteen (15) minutes before transfer.
b. if IV Narcan is administered, the patient will remain in the PACU for an additional ninety (90) minutes.

c. nausea and vomiting is not persistent, has not occurred within fifteen (15) minutes prior to expected transfer, and the patient has not recently been medicated for the nausea and vomiting, then the patient can be transferred.
d. at the time of transfer the patient has a pain level of three (3) or less (on a scale of 0 to 10) or a self tolerable pain level for their own comfort.
e. if any of the above symptoms persist the anesthesiologist on call is consulted and can clear the patient for transfer.

8. Avoiding complications from surgery:

   a. the patient can be transferred if there is no evidence of specific surgical complications, i.e. evidence of accelerating hemorrhage, disconnected drainage tubes, etc.

   b. all surgical complications have been reported to the surgeon and appropriate treatment has been initiated.

9. The patient is transferred when all the above transfer criteria have been met and with the following professional approval. A Registered Nurse will sign on the FORM DA 4700, TAMC OP 206-2, TAMC Post Anesthesia Care Assessment and Planning sheet following and therefore agreeing with the statement "This patient has met the criteria under the PARS system to be cleared from the Post Anesthesia Care and return to ward ___ via bed at __*(Time)*__. The Registered Nurse's signature is for and with the approval of Chief, Anesthesia and Operative Services.

PACU SOP B-7 POST ANESTHESIA RECOVERY SCORE

VI. PROCEDURE:

A. Post Anesthesia Recovery Score (PARS) criteria used in the PACU and found on FORM DA 4700, TAMC OP 206-2 / 1 FEB 96, Post Anesthesia Care Assessment and Planning.

1. Consciousness

a. Fully Awake	2
b. Arousable	1
c. Non-Responsive	0

2. Color

a. Pink	2
b. Pale, Dusky	1
c. Cyanotic	0

3. Circulation

a. BP within 20 Pre-op	2
b. BP within 20-30 Pre-op	1
c. Above / Below 30	0

4. Respiration

a. Deep Breath and Cough	2
b. Deep Breath only	1
c. Shallow and Labored breathing	0

5. Activity

a. Moves 4 Extremities	2
b. Moves 2 Extremities	1
c. Moves 0 Extremities	0

APPENDIX G

Ambulatory Surgical Center Discharge Guidelines

SURGICAL ADMISSION CENTER
TRIPLER ARMY MEDICAL CENTER
HAWAII 96859-5000

SAC SOP 14

May 1999

AMBULATORY SURGICAL CENTER DISCHARGE GUIDELINES

PURPOSE: To establish standard guidelines for discharge from the Ambulatory Surgical Center (ASC).

SCOPE: All nursing and medical personnel caring for patients in the ASC post-anesthesia area.

POLICY:

1. Patients received into the post-anesthesia area for observation and care following surgical intervention concurrent with the administration of anesthetic agents.

2. Evaluation of these patients for discharge is concurrent with management policies written into the current edition of the JCAHO Accreditation Manual for Hospitals.

3. Post-anesthesia care in the ASC is staffed to provide observation and care. Nursing staff includes registered nurses to provide direct patient care, evaluation, and discharge.

PROCEDURE:

1. Patients are released after meeting the discharge criteria.

2. Criteria for discharge assessment of patients from the post-anesthesia area include:

a. The patient regains consciousness, is oriented to time and place, and is verbal according to normal developmental age.

b. The patient's airway is clear and the danger of vomiting and aspiration is past.

c. Circulatory and respiratory vital signs are stable and normal for each patient.

d. Patient verbalizes manageable pain level.

SURGICAL ADMISSION CENTER
TRIPLER ARMY MEDICAL CENTER
HAWAII 96859-5000

SAC SOP 14

May 1999

4. When the Post-anesthesia Recovery Room Score (PARS) on ASC Post Operative Nursing Document (DA Form 4700-TAMC OP 340) is 8 to 10. This PARS covers the consciousness, color, circulation, respiration, and activity of the patient.

5. The patient tolerates fluids.

6. Patient desires discharge, ambulates, and urinates and verbalizes a manageable pain level..

7. Documentation of readiness for discharge is documented on TAMC OP 340.

8. The nursing assessment, evaluation, and verbalization of discharge instruction understanding given is documented in the nursing notes (TAMC OP 340).

APPENDIX H

Home Questionnaire

Home Questionnaire

We will be calling you sometime tomorrow to see how you are doing after surgery. Please take the time to fill out this questionnaire prior to us calling you Whether we are able to contact you or not, mail this completed form back to us within 2-3 days with the self-addressed and stamped envelope provided. Thank you again for participating in our study.

6 hours after surgery: That time will be at_____.

1. Rate your pain using the numbered scale (0-10) that you used earlier today after your surgery in the hospital. SCORE is_____.

2. If you are having pain, where is the pain located on your body?

_____

3. Describe what your activity is (for example: walking around the house, playing with your children, sleeping, eating).

_____.

Bedtime: Write down the time that you go to bed_____.

1. Rate your pain using the numbered scale (0-10) that you used earlier today after your surgery in the hospital. SCORE is_____.

2. If you are having pain, where is the pain located on your body?

_____.

3. Describe what your activity is.

_____.

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

1. Did you take any of the pain medicine, prescribed by your doctor, from the time that you left the hospital until bedtime? YES NO

2 If you answered yes to the above question, how many pain pills did you take, and at what times? _____

3. Did you take any other medicines from the time you left the hospital until bedtime (including any over the counter medications)? YES NO

4. If you answered yes to the above question, what did you take, and at what time?

_____

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

_____

6. Did you have any nausea? YES NO

7. Did you vomit? YES NO

Answer the following questions regarding your surgery/anesthesia service:

1. How was your surgical experience?

2. Is there anything we could have done differently?

3. How was your overall satisfaction with pain control?

4. What was it like to be in this study?

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

APPENDIX I

Postoperative Analgesia/Nausea and Vomiting Order Sets

1 NRS q-MISCELLANEOUS *STAT PRIORITY One Time QH {TYLENOL 120 MG SUPP. X 1 PRN FOR PAIN}
2 NRS q-MISCELLANEOUS *STAT PRIORITY One Time {ACETAMINOPHEN (TYLENOL) <ORAL> 325 MG QH {QD} X1 FOR PAIN}
3 NRS q-MISCELLANEOUS *STAT PRIORITY One Time {ACETAMINOPHEN--PO 160MG/5ML SUSP (TYLENOL) <ORAL>5ML QH {QD} PRN HA/PAIN}
4 IVF *ASAP* RINGERS LACTATED--INJ SOLN 1000ML 1000ML/HR {FOR LOW URINE OUTPUT OR HYPOTENSION NOTIFY ANESTHESIA AFTER BOLUS FOR EFFECT.}
5 IVF *ASAP* SODIUM CHLORIDE 0.45%--IV 250ML INJ 1000ML 1000ML/HR {FOR LOW URINE OUTPUT OR HYPOTENSION NOTIFY ANESTHESIA AFTER BOLUS FOR EFFECT}
6 IVF q-RINGERS LACTATED--INJ SOLN 1000ML 50ML/HR {TKO OR AS ORDERED BY ANESTHESIOLOGIST.}
7 IVF q-SODIUM CHLORIDE--INJ 0.9% SOLN 1000ML 50ML/HR {TKO OR AS ORDERED BY ANESTHESIOLOGIST.}
8 IVP *ASAP* MORPHINE SULFATE <PUSH> 2.5MG NOW X4 One time {GIVE 2.5MG Q 5MIN PRN PAIN NOT TO EXCEED 10MG,SEE PACU FLOWSHEET FOR TIMES}
9 IVP q-*ASAP* LABETALOL (NORMODYNE) (TRANDATE) <PUSH> 5MG NOW One time {5MG INCREMENTS Q 5 MIN TITRATE TO SBP>110, DBP>70, HR>55,SEE PACU FLOWSHEET}
10 IVP q-*ASAP* FENTANYL (SUBLIMAZE) <PUSH> 100MCG Q2H X4 One time {GIVE 25MCG INCREMENTS Q5MIN NOT TO EXCEED 100MCG IN 2 HOURS.}
11 IVP *STAT* DROPERIDOL (INAPSINE) <PUSH> 0.625MG X1 PRN {PRN NAUSEA AND VOMITING IF SBP >100}
12 IVP q-*STAT* KETOROLAC (TORADOL) <PUSH> 30MG NOW Now {GIVE x1 for pain. }
13 IVP q-*STAT* ONDANSETRON HCL (ZOFRAN) <PUSH> 4MG NOW Now {give q15min prn nausea vomiting. May repeat x 2.}
14 IVP q-*STAT* METOCLOPRAMIDE (REGLAN) <PUSH> 20MG NOW Now {MAY REPEAT X 1 IN 30MIN}
15 IVP q-*STAT* MEPERIDINE HCL(DEMEROL) (DEMEROL) <PUSH> 25MG NOW Now {Q 5 MIN FOR PAIN AND SHIVERING, NOT TO EXCEED 100MG}
16 IVP q-*STAT* MIDAZOLAM <PUSH> 1MG NOW Now {(VERSED) 1mg Q5min not to exceed 5mg in 2 hours for anxiety.}
17 IVP *STAT* DOLASETRON (ANZEMET) (ANZEMET) <PUSH> 12.5MG One time {MAY GIVE PRN X 1 FOR NAUSEA/VOMITING}

APPENDIX J

Standard Operating Procedure for Medication Administration in the Surgical Admission Center

SURGICAL ADMISSION CENTER
TRIPLER ARMY MEDICAL CENTER
HAWAII 96859-5000

SAC SOP 23

May 1999

MEDICATIONS IN THE SURGICAL ADMISSION CENTER

PURPOSE: To provide guidelines for the administration, location and storage of medications in the Surgical Admission Center (SAC).

SCOPE: All nursing personnel assigned to the SAC.

POLICY:

1. Medications are stored in the SAC Medication Room (Room 6B516). No medication are stored in patient rooms. Narcotics are stored within the double locked narcotic box, located in the Medication Room. Medications are given on a as needed basis.

2. Military and civilian licensed nurses (RN, and LPN) are authorized to administer medicatior in the SAC. (See Annex 1 for list of drugs currently stocked.)

3. EMLA Cream (lidocaine 2.5% and prolocaine 2.5%) is for pediatric patients ages seven through seventeen, unless otherwise ordered by anesthesia. Identified patients are issued one 5g tube and transparent dressings. The SAC RN instructs the patient/guardian how to apply the cream and dressings according to the manufacturers instructions. This teaching is documented on the Patient/Family Teaching Flow sheet (DA Form 4700, TAMC OP 358.)

4. For expected postoperative pain in the ASC, the patients prescribed pain medication (ordered by the surgeon in CHCS, usually picked up by the patient's escort) is administered, as ordered, by an RN or LPN/91C. This is documented on the ASC Post operative Nursing Document (DA Form 4700, TAMC OP 340), as well as effectiveness.

5. For unrelieved pain in the ASC, the SAC nurse anesthetist or anesthesiologist (during duty hours) or the anesthesiologist on call (after duty hours) is consulted. They may order Toradol IVP from the ASC/RR order set, which is to be administered by an RN. This is annotated on the DA Form 4700 OP 340, with effectiveness documented.

a. Registered nurses assigned to the SAC must participate in a IVP Drug Familiarization program, successfully pass a verification test (score 80%or above), and be observed by an anesthesia provider or another "verified" ASC RN three time before she/he is allowed to administer an authorized IVP medication in the ASC (Annex 2).

6. For postoperative nausea and vomiting in the ASC, the SAC nurse anesthetist or anesthesiologist (during duty hours) or the anesthesiologist on call (after duty hours) is consulted. An RN may give an anti-emetic as ordered from the ASC/RR order set, which includes Inapsine, Reglan, and Zofran. This is documented on the DA Form 4700 OP 340, as well as the drugs effectiveness.

7. The emergency drug supply is kept in the crash cart. Central Materiel and Supply and Pharmacy personnel replenish supplies/drugs used from the crash cart, if opened, or if expirations are noted.

SURGICAL ADMISSION CENTER
TRIPLER ARMY MEDICAL CENTER
HAWAII 96859-5000

SAC SOP 15

May 1999

PATIENT PRESCRIPTIONS

PURPOSE: To establish guidelines for the handling of prescription medications for patients in ASC.

POLICY:

1. Prescriptions for post-operative home use are written (in CHCS) for patients by their surgeons after surgery to allow enough time for pick-up.

2. The prescription is picked up in the Outpatient pharmacy by the family member, escort or ASC staff (with the patient's ID card).

3. Prescribed medications are not given to the patient in ASC until authorized by the RN.

4. Nursing discharge instructions include the name of the medication, the purpose, the dosage, and effects.

APPENDIX K

TAMC Human Use Committee Approval Letter

MCHK-CI (40-38a) OCT 2 5 1999

MEMORANDUM FOR CPT Patricia S. Harm, AN, Department of Health Education and Training (ATTN: MCHK-HE), Tripler AMC, HI

SUBJECT: Approval to Initiate More Than Minimal Risk Study

1. Your clinical investigation project entitled "TAMC 39H99: A Comparison of Postoperative Pain with Preemptive Administration of Intravenous Ketorolac Versus Oral Ibuprofen in Patients Undergoing Interval Laparoscopic Bilateral Tubal Sterilization" completed required review by the Institutional Review Board (IRB) on 27 Sep 99 and is approved to start immediately.

2. **Please note that this is NOT an approval to receive extramural resources** (ie, personnel, drugs, supplies, equipment, money, and gifts from any source outside of TAMC) **nor an indication of guaranteed funding from the Department of Clinical Investigation**. 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. You must coordinate extramural resource approvals with the Department of Clinical Investigation, Bldg 40, 433-6709.

3. Your study has more than minimal risk, and the medical monitor assigned is LTC Lynn F. Dahl, MC. (S)He has the authority to require changes to your study or even suspension of your research to protect the safety of the volunteers. It is your responsibility to keep the medical monitor continuously informed of the status of your work and in particular to immediately report any sign or symptom suggesting adverse effect or increased risk of a volunteer, whether or not that increased risk is thought to be due to the research. The medical monitor's recommendations and requests are to be complied without failure or delay; if you cannot comply, suspend all research on this protocol immediately and notify me directly. Once a safety measure is instituted, it may not be dropped without review of the Human Use Committee and command decision.

4. Should any of the volunteers experience signs or symptoms of adverse effects or illness, you must insure immediate medical referral to the appropriate Tripler AMC health care team. You must document all such occurrences, whether or not caused by your research, and report them to the Human Use Committee. Your medical monitor will advise you whether or not that report can wait for your annual review.

5. You must report your study findings, including number of patients and adverse effects, to the Human Use Committee prior to one year from this date (or earlier if required to do so by the medical monitor). You must also report your study in the TAMC Annual Report of Clinical Investigation Activities. You will be given full instructions, including schedule of reports, from the Chief, Clinical Investigation, 30 days prior to any report suspense.

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

6. Your study and its documentation, including list of volunteers and copies of the volunteers' informed consent statements, are subject to inspection at any time by your chain of command and by such inspectors of official audit agencies as obtain prior consent from this command. You must maintain your records such as to facilitate such inspections.

7. Any public presentations or publications of your work must receive prior clearance of this command. This includes academic lectures given outside TAMC, abstracts submitted to professional meetings, 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, notify the Chief, Clinical Investigation, at 433-6709.

Encl

for JOHN R. AGUILAR
CAPT, MC, USN
Deputy Commander for Clinical Services
Chair, Human Use Committee

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