LOCALLY APPLIED KETOROLAC AND BUPIVACAINE WITH EPINEPHRINE FOR THE CONTROL OF POSTOPERATIVE PAIN IN BREAST AUGMENTATION PATIENTS

by

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ABSTRACT

One of the difficulties that continues to challenge reconstructive and aesthetic surgeons is postoperative pain control. Developments in anaesthesia have increased the understanding of pain and it is now accepted that there is a role for pre-empting it. Research with systemic non-steroidal anti-inflammatory drugs and local anaesthetics has been encouraging.

The use of locally applied non-steroidal anti-inflammatory drugs in combination with local anaesthetics has not been studied. The objective of this study was to test the effectiveness of locally administered, intraoperative Ketorolac and Bupivicaine with epinephrine at reducing pain in the first two-hours of the postoperative period. Ethical approval was obtained from the Ethics Review Board of the Okanagan / Similkameen Health Region through the Kelowna General Hospital and the Medical Director of the Okanagan Plastic Surgery Center.

The study was designed as a prospective, randomized, triple-blind, clinical trial. One hundred consecutive breast augmentation patients were enrolled and informed consent was obtained from each patient. A standard anaesthetic protocol and surgical procedure were followed. The intervention was divided into four groups of twenty-five patients that received either normal saline, Ketorolac only, Bupivicaine only or Ketorolac and Bupivicaine. The primary outcome was pain as measured by the Visual Analog Pain Scale. The secondary outcome was time spent in the recovery room. Other variables were considered for their effect on postoperative pain. All patients completed the study. The power of this study was 0.90 and confidence intervals of 95% were used to determine significance.

The findings of this study allow rejection of the null hypothesis and support the alternate hypothesis that in women undergoing primary augmentation mammaplasty, intraoperative irrigation of Ketorolac combined with Bupivicaine with epinephrine into the surgical wound reduced pain in the postoperative period.

It did not appear that anaesthesiologist, anaesthesia time, surgeon, OR time, difficulty of dissection or implant size had a significant impact on postoperative pain. Time in the recovery room was not different between the current standard of care and the Ketorolac and Bupivicaine patients. However, there was a trend that Ketorolac and Bupivicaine patients did spend less time in the recovery room than the Bupivicaine only patients.
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CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1 INTRODUCTION

The introduction of the silicone breast implant in 1963 marked the development of breast augmentation as we know it today. The last decade has been witness to a dramatic increase in the number of cosmetic breast procedures performed. This type of aesthetic surgery lends itself well to outpatient or daycare surgery, where the patient is discharged home several hours after the procedure. One of the major issues in the postoperative period is pain control. Previous postoperative pain management strategies for patients in the recovery room have focused on using incremental doses of opioids in an attempt to reduce already established pain. However, high doses of opioids are associated with nausea and sedation which can in turn increase postoperative complications and prolong the discharge-to-home process.

This thesis project evaluates the role of pre-emptive analgesia in the treatment of postoperative pain. Experimental evidence has verified that local anesthetics given intraoperatively reduce the perception of pain and the need for opioids postoperatively. Systemically administered Ketorolac has also been shown to be an effective pre-emptive analgesic. The inference is that locally applied Ketorolac may also serve as an effective pre-emptive analgesic. However, locally applied Ketorolac has not previously been studied.

The objective of this thesis project was to test the effectiveness of locally administered, intraoperative Ketorolac and Bupivicaine with epinephrine at reducing pain in the first two-hours of the postoperative period in patients undergoing breast augmentation surgery.

1.2 PRE-EMPTIVE ANALGESIA

Postoperative analgesia is an important consideration in patients undergoing outpatient surgery. Until recently, pain has been viewed as the result of the passive transmission of a signal from the periphery to the spinal cord and on to the pain center in the brain. Patients were typically transported to the recovery room with entrenched pain; the management of which consisted of incremental doses of opioids. This approach did not provide adequate relief of pain, in part, because it focused on treating the pain only after it was well established.

This outdated conceptualization of pain has been discarded in light of experimental and clinical evidence that demonstrates that C-fibre activation from brief noxious stimuli or frank injury induced enduring alteration in central neural function. Using a decerebrate rat model, it was shown that afferent impulses initiated a prolonged widespread increase in reflex excitability and interneurone excitability. When stimulation was applied to deep tissue, the hyperexcitability was marked. Wall et al. also showed that a brief but maximal injury discharge was generated with the cutting of a peripheral nerve which triggered prolonged spinal cord hyperexcitability. These changes
Persist even after the offending stimulus has been removed or the injury healed. The clinical relevance of this data is unclear at this point.

In 1913, Crile (as cited in Katz 1993) was the first to suggest that postoperative pain may be amplified by the noxious events induced at the time of surgery. However, it was not until 1991 that Woolf coined the term "pre-emptive analgesia" after basic science research over the previous decade demonstrated that preoperative opioids and local anesthetics reduced central sensitization and consequently postoperative pain. Wolfe and Wall wrote that once established, central sensitization required large doses of opioids to suppress it, and they believed that preoperative narcotics could prevent it altogether. It has since been recognized that the nociceptive neuron blockade of systemic opioids is insufficient to block central sensitization. Central sensitization or hyperexcitability causes subsequent amplification of inputs from the wound and leads to increased postoperative pain. The idea that this could be avoided by disrupting the transmission of noxious perioperative inputs is engaging.

General anesthesia is defined in Stedman’s Medical Dictionary as “a loss of ability to perceive pain associated with the loss of consciousness produced by intravenous or inhalation anesthetic agents.” General anesthesia is accomplished by providing the smallest anesthetic dose consistent with the patient’s comfort and safety while immobility is produced by paralyzing agents. However, while general anesthesia may attenuate the massive afferent stimulation produced by surgery, it does not block it. In contrast, the spinal cord receives few or none of the afferent impulses set off during surgery when under regional anesthesia.

There are three distinct phases to the perioperative period. The interaction of these aspects contributes to the development of acute postoperative pain. Preoperatively, the patient can experience anxiety and stress as well as pain (starting of intravenous lines). Intraoperatively, the noxious stimuli arise mainly from the surgical procedure (incision, dissection of skin, muscle, nerve and bone, retraction, etc). Postoperatively, the inflammatory response and ectopic neural activity (in the case of post surgical nerve injury) contribute to the peripheral stimulation. By recognizing the impact of the noxious inputs and subsequently minimizing them, central sensitization can be prevented, resulting in decreased pain intensity and lower analgesic requirements even after the analgesic effects of the pre-emptive agents have worn off.

The demonstration of this dynamic interplay between peripheral and central mechanisms is the topic of a considerable amount of research as reported in the Anesthesiology literature. The result is that the practice of treating pain after it has been established is slowly being supplanted by a preventative approach.

1.3 LOCAL ANESTHETICS

The clinically useful local anesthetics are either amino amides or amino esters. Local anesthesia is the condition that results when the nerve conduction of sensory information from the periphery to the central nervous system is blocked. In the nonionic state, the
local anesthetic passively diffuses through the cell membrane where it becomes charged and blocks the sodium channel within the neuron. Blockage of the voltage-dependent sodium channels reduces the influx of sodium ions and thereby prevents the depolarization of the membrane (conduction of the action potential). These agents can be applied topically, injected intra/subcutaneously, injected in the area of major peripheral nerves or injected into the spinal cord.\(^{(17)}\)

The activity of the agent is related to its lipid solubility, protein binding, pKa and vasodilator activity.\(^{(18)}\) In order to have an effect, the local anesthetic molecule must first pass through the lipophilic nerve cell membrane. In vitro lipid solubility or hydrophobicity is the primary determinant of anesthetic potency. In a clinical setting, the vasodilatory effect and tissue redistribution also play a role. The pKa, dose and concentration of local anesthetic administered are the determinants of onset of action. Again clinically, the result is slightly different in that dose is the primary determinant of satisfactory anesthesia.\(^{(19)}\) The duration of the local anesthetic is governed by the vasodilatory effects of the individual agents. With increased vasodilation, more local anesthetic is absorbed into the vascular system. Addition of a vasoconstrictor will prolong the duration of action (discussed in the next section). Bupivicaine is a high potency, long-duration local anesthetic.\(^{(20)}\)

The most common method of achieving local anesthesia, infiltration anesthesia, is by injecting it into the operative site without selectively blocking a specific nerve. Injection may be intradermal, subcutaneous or both and the duration of action will vary. The infiltration process can cause a painful, burning sensation with injection into the dermis being the most painful. When possible, as in open wounds, local irrigation of the agent can be effective and circumvents the most painful aspect of the process of local anesthesia.\(^{(21,22)}\) In the role of a pre-emptive anesthetic, local anesthetics have been shown to significantly lengthen the pain-free period after surgery.\(^{(23)}\) Bupivicaine is the logical choice as it has a pKa of 8.1 and a relatively long half-life of 2.7 hours while still being comparatively inexpensive.\(^{(19)}\)

When toxic reactions to local anesthetics occur, they are almost always associated with inadvertent intravascular injection or administration of excessively large doses. The toxicity of these agents affects the central nervous system and the cardiovascular system. Local anesthetics freely cross the blood-brain barrier and initially result in depression of the cortical inhibitory pathways allowing the excitatory pathway to act unopposed. At higher blood levels, there is a generalized central nervous system depression and eventually loss of consciousness, apnea and grand mal seizures.\(^{(24)}\) Cardiovascular toxicity is the direct result of myocardial depression with effects on the vascular smooth muscle as well as the conducting system. The risk of toxicity from a local anesthetic can be minimized by the local irrigation of a safe dose.

1.4 VASOCONSTRICTORS

Another factor affecting the performance of a local anesthetic is the addition of a vasoconstrictor. When a local anesthetic is utilized for local infiltration or peripheral
nerve blocks, the duration of action can be markedly prolonged with the adjunctive epinephrine. Vasoconstrictors decrease the rate of vascular absorption of local anesthetic molecules thereby increasing the number of molecules available to act on the nerve cell membrane. This effect also results in lower blood levels which lower the risk of systemic toxicity.

Bretteville-Jensen was the first to describe the beneficial effect of reduced blood loss with a vasoconstrictive agent in breast reduction. Since then, the vasoconstrictor effects of adrenaline and noradrenaline have been shown to reduce perioperative blood loss in several plastic surgery procedures. Postoperative morbidity and requirement for blood transfusion have also been show to be reduced with adrenaline. With the current heightened awareness of blood-related transmissible diseases, this offers a definite advantage.

Although minimal side effects are seen with vasoconstrictors when used in appropriate doses, reactive hyperemia can be seen as well as hypertensive crisis and cardiac arrhythmia/arrest if injected intravascularly. There have been reports of ischemic necrosis when combinations of adrenaline and local anesthetic were used in end arteries although recent publications have refuted this.

1.5 NON-STERIODAL ANTI-INFLAMMATORY DRUGS

In response tissue injury and other stimuli, phospholipases in the cell membrane are activated leading to the production of arachidonic acid from membrane lipid. Once synthesized, the arachidonic acid is metabolized by one of two enzymes. Lipoxygenase converts it into straight chain products which will eventually be converted into leukotrienes. Alternatively, the enzyme cyclooxygenase (Cox) may cyclize the arachidonic acid resulting in the production of prostacyclin, prostaglandin or thromboxane. The Cox enzyme has been found to have at least two different isoforms and others likely exist. The prostaglandins produced by Cox I are thought to be important for a variety of normal physiologic processes in various tissues throughout the body. Primarily found in lymphocytes, polymorphonuclear and other inflammatory cells, Cox II synthesizes products that play a salient role in inflammation. Arachidonic acid metabolism by Cox II produces mainly thromboxane in platelets and prostacyclin in the endothelial cells of vessels.

Both isoforms of the Cox enzyme are inhibited by non-steroidal anti-inflammatory drugs (NSAID). The resulting decrease in synthesis of prostaglandins describes the peripheral anti-inflammatory action of the NSAID’s. The prostaglandins themselves do not cause pain. They act at the site of injury to sensitize the receptors to a number of neurochemicals. Thus, the peripheral activity of NSAID’s that is usually termed analgesic is better expressed as anti-hyperalgesic. Yaksh et al. studied the mechanism of action of the NSAID’s and found that the anti-inflammatory and analgesic effects could be dissociated. Combined with the evidence that NSAID’s may produce a non-anti-inflammatory analgesic action through inhibition of Cox in the spinal cord, it raised the possibility of a central site of action for these agents.
Peripherally, the pre-emptive analgesic effect of NSAID’s is due to an attenuated inflammatory response that reduces peripheral sensitization and its effects on the spinal nociceptive processing, including the induction and maintenance of central sensitization. Centrally, the pre-emptive analgesic effect of NSAID’s is attributed to a prevention of spinal prostanoid synthesis thus reducing pre and post-synaptic release of neurotransmitters. The combined central and peripheral actions prevent or at least significantly attenuate central sensitization. Clinically, the effect should be to reduce the immediate post-surgical pain and therefore the requirements for analgesics in the postoperative period.

These effects were recently demonstrated in a study by O’Hanlon et al. The study was prospective, randomized and single-blind. In that study, the researchers compared patients undergoing ambulatory breast biopsy that received a 20mg intravenous dose of tenoxicam either 30 minutes prior to surgery or at the induction of anesthesia. No premedication was administered and all patients received 2mg/kg of propofol and 5ug/kg of alfentanyl. At the end of surgery, but prior to emergence, all patients’ wounds were infiltrated with 10ml of 0.5% Bupivicaine. For a four hour period after surgery, pain and analgesic consumption were recorded. There were significant differences in pain, measured with a visual analog pain scale, at all time points (30, 60, 120 and 240 min), as well as in time to first request for postoperative analgesics and in the number of patients requiring additional analgesia in favor of the patients that received the tenoxicam earlier.

In North America, tenoxicam is not yet approved by the governing agencies for use in humans. In fact, the selection of intravenous NSAID’s is limited to a single drug, Ketorolac. In the early nineties, Roche introduced Ketorolac (Toradol) for use as a parenteral NSAID with strong analgesic activity. The analgesic efficacy of Ketorolac has been extensively evaluated in the postoperative setting, in both hospital inpatients and outpatients, and in patients with various other acute pain states. Two features have limited its clinical utility: tendency to elicit kidney failure and inability to produce complete analgesia. Most NSAID’s are weak acids (pKa 3-5) and thus become concentrated in acidic tissues such as injured and inflamed tissues. The pKa for Ketorolac is 3.5. Because the drug is nonirritating to the tissue and systemic application has not resulted in increased tissue injury, the local application was considered safe. Local administration enhances its analgesic efficiency while lowering the potential for systemic complications. The acquisition cost of Ketorolac is greater than that of morphine or pethidine (meperidine). However, the higher cost of Ketorolac is offset since treatment with Ketorolac results in a reduced hospital stay and significant cost savings in comparison with opioid therapy. The tolerability profile of Ketorolac parallels that of other NSAID’s. The most clinically important adverse events affect the gastrointestinal tract and / or renal or hematological function.

Ketorolac has proven to be a strong analgesic with a tolerability profile that resembles that of other NSAID’s. When used in accordance with current dosage guidelines, this drug provides a useful alternative, or adjuvant, to opioids in patients with moderate to severe pain.
The respective pharmaceutical representatives for the Ketorolac and Bupivicaine in Canada were contacted individually. Both were confident enough on an informal basis to comment that their product would be stable in the mixture. In a personal communication, the Ketorolac (Roche) representative went so far as to discuss assays of Ketorolac after mixing the medication with the appropriate volume of Bupivicaine (Abbott). They indicated that they had found the Ketorolac to be stable.

1.6 VISUAL ANALOG PAIN SCALE

Pain is a common problem in the postoperative period of most surgical procedures. The complexity of pain is reflected in its decidedly personal nature and the experiences and behaviors associated with it. Effective management of postoperative pain is dependent on having an accurate measure of the patient's pain intensity. The measurement yields information not only on the degree and location of pain, but also determines the effectiveness of a particular therapeutic intervention at producing the desired clinical result. Therefore, an accurate and reliable method of pain measurement is an essential component of any study undertaken with the goal evaluating a pain management protocol.\(^{55}\) The characteristics of an ideal pain measurement tool were described by Gracely and Dubner\(^{56}\) and found in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of an Ideal Pain-Measurement Tool</th>
</tr>
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<tbody>
<tr>
<td>1. Has ratio-scale properties</td>
</tr>
<tr>
<td>2. Is relatively free of biases inherent in different psychophysical methods</td>
</tr>
<tr>
<td>3. Can separately assess the sensory-intensive and affective dimensions of pain</td>
</tr>
<tr>
<td>4. Provides immediate information about the accuracy and reliability of the subject's performance on the scaling responses</td>
</tr>
<tr>
<td>5. Is useful for both experimental and clinical pain and allows reliable comparison between both types of pain</td>
</tr>
<tr>
<td>6. Is reliable and generalizable</td>
</tr>
<tr>
<td>7. Is sensitive to changes in pain intensity</td>
</tr>
<tr>
<td>8. Is simple to use for both clinical and research settings</td>
</tr>
<tr>
<td>9. Provides a basis for the comparison of human psychophysical responses to nociceptive neural responses obtained in neurophysiologic experiments</td>
</tr>
</tbody>
</table>

From Pain 1981;11:109-120.\(^{56}\)
have the same meaning for all individuals. A 1992 literature review of self-report scales by Jensen et al. demonstrated a number of limitations of verbal descriptive scales including problems with scoring procedures and patient selection of verbal descriptors.

Visual analogue scales, among the most commonly used measures of pain intensity, use a line to represent the continuum of the pain experience. First described more than three-quarters of century ago (as cited in an article by Maxwell), the instrument consists of a line of a defined length that can be perceived as a unit by the patient. The distance from the end of the scale to a point marked by the patient on the line represents the severity of his or her pain. The line may be vertical or horizontal and is usually ten centimeters in length. The anchor points are zero and 10 and the descriptions of "no pain" and "worst pain imaginable" have been found to give the best range of results. However, these verbal descriptions can be varied depending on what the investigator is trying to measure. If descriptive terms are placed at intervals along the line, it becomes a graphic rating scale. As some patients prefer certain numbers, it is generally agreed that integers should not be added to the line. While graphic rating scales have their proponents, recent attempts at standardization of pain assessment have focused on visual analog scales. The rationale for standardization is found in Table 2. Commonly used in research, visual analogue scales have been found to be valid and reliable. The outcome measure selected was the visual analog pain scale (VAPS). This instrument has been validated in patients undergoing breast surgery and meets several of the characteristics of an ideal pain measurement tool including: sensitive to changes in pain intensity, ratio-scale properties, relatively free of bias and is reliable and generalizable.

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Table 2. Rationale for standardization of clinical pain rating

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Minimize patient/family confusion regarding report of pain intensity</td>
<td>Create stress for individuals who have difficulty understanding translation of pain intensity to a numerical scale</td>
</tr>
<tr>
<td>Promote consistency in evaluation</td>
<td>Create stress for individuals who are reluctant to use the extreme points of the scale, perhaps because they never want to be &quot;extremists&quot;</td>
</tr>
<tr>
<td>Clarify communication</td>
<td>May require more time for patient education and comprehension</td>
</tr>
<tr>
<td>Reduce potential impact of accessor's bias</td>
<td>Potential bias of reliable what pain &quot;should look like&quot; associated with use of faces scale</td>
</tr>
<tr>
<td>Provide greater sensitivity and accuracy in assessment</td>
<td>Potential for cultural bias associated with the use of faces scales</td>
</tr>
<tr>
<td>Simplify the process and enable collection of comparative data</td>
<td></td>
</tr>
<tr>
<td>Contribute psychometrically valid and reliable data</td>
<td></td>
</tr>
</tbody>
</table>

From Cancer Nursing 21;1:46-49.
1.7 AUGMENTATION MAMMAPLASTY

The 1990's were a controversial time for cosmetic augmentation mammaplasty (breast augmentation surgery). As the decade began, the popularity of the procedure was growing and an increasing number of women were seeking cosmetic breast augmentation, perhaps owing to the mass media portrayal of the large breast and lean body ideal. At the same time, thousands of women with silicone breast implants were filing reports with the Food and Drug Administration (FDA) claiming physical symptoms and nonspecific illness. These reports were the basis on which the then commissioner David Kessler banned the use of silicone implants. Kessler cited a lack of research demonstrating either an acceptable safety profile or a psychological benefit as the justification. Shortly thereafter and in response to a number of class action lawsuits, the largest manufacturer of silicone breast implants in North American (Dow Corning), filed for bankruptcy. Despite this, the number of women undergoing breast augmentation with saline implants dramatically increased. In the intervening years, several articles appeared in peer-reviewed journals that failed to demonstrate any relationship between silicone breast implants and connective tissue or autoimmune disorders.

Finally, in 1999, the Institute of Medicine released its “Safety of silicone breast implants” report which had as its major conclusion, “silicones and other substances known to be in breast implants do not provide a basis for health concerns.” After reviewing over 3300 articles and reports and hearing from experts in industry and academia as well as women with silicone implants, they found no correlation between silicone implants and autoimmune diseases or other health problems. The report also found no relationship between implants and breast cancer or implants and silicone in milk.

The number of women with breast implants in the United States currently exceed two million and the number of women requesting breast augmentation continues to increase. Sarwer et al. found that the members of the American Society of Plastic Surgeons performed 132,378 cosmetic breast augmentations in 1998, a 306% increase from 1992. The same statistics were not available in Canada. Augmentation mammaplasty has become the most commonly performed cosmetic breast procedure.

The procedure requires that a pocket suitable for implant placement be created deep to the muscle and this is accomplished primarily by blunt dissection or cautery. The dissection partially detaches the sternal origins of the pectoralis major muscle below the third intercostal space. The costal origins of the pectoralis major muscle may also be also detached. This dissection creates significant pain in the postoperative period. Currently, plastic surgeons use only normal saline to irrigate the breast implant pocket prior to placement of the implant. Until now, the pain was managed postoperatively with increasing doses of narcotic analgesics. With the recent developments in the field of preemptive analgesia, the question arises as to whether or not there is a role for irrigating local anesthetics with epinephrine and / or NSAID's into the implant pocket.
1.8 INFORMED CONSENT

A clear set of guidelines has been formulated by the Institutional Research Review Committee of the Kelowna General Hospital and Okanagan / Similkameen Health Region. First and foremost, the consent form should be written in the prospective participant's preferred language in lay terms at an appropriate level. Complex medical terminology should be accompanied by a simple explanation. The consent form should not include a statement releasing the researcher, sponsor, institution or any agent thereof from liability from negligence and must clearly identify who those persons are.

A copy of the written informed consent that was given to the patients in this study is included in Appendix A.
CHAPTER 2: EXPERIMENTAL

2.1 OBJECTIVE

The objective of this study was to test the effectiveness of locally administered, intraoperative Ketorolac and Bupivicaine with epinephrine at reducing pain in the immediate postoperative period.

2.2 NULL HYPOTHESIS

The null hypothesis was that in women undergoing primary augmentation mammaplasty, intraoperative Ketorolac combined with Bupivicaine with epinephrine irrigated into the surgical wound would not significantly change the pain in the postoperative period compared to those irrigated with normal saline only. The alternate hypothesis was that in women undergoing primary augmentation mammaplasty, intraoperative Ketorolac combined with Bupivicaine with epinephrine irrigated into the surgical wound would reduce pain in the postoperative period.

2.3 PILOT STUDY

A pilot study was performed at the Okanagan Plastic Surgery Center (OPSC). Ten patients undergoing primary, bilateral augmentation mammaplasty were randomly assigned to receive either standard treatment (normal saline irrigation) or Ketorolac / Bupivicaine / epinephrine combination. The pilot study was prospective. Only the patients were blinded. The anesthesiologists used standard medications to induce and maintain anesthesia. The same operative procedure was used in all ten cases with the implants being placed submuscularly. Postoperatively, all of the patients did well and there were no complications. Pain was controlled with intravenous narcotics and oral acetaminophen and codeine. A visual analog pain scale with the anchor points zero and ten was used to measure the pain intensity.

In the group that received that standard treatment, the average implant size was 360cc compared to 380 cc for the experimental group. The average reported pain intensities immediately postoperatively, at one half hour, one hour and at the time of discharge were 0, 5.2, 3.6 and 3 for the standard group and 0, 0, 0 and 0.4 for the experimental group respectively. The mean time spent in the recovery room for the standard group was 280 minutes and 133 minutes for the experimental group.

The pilot study provided valuable insight into the design, organization and administration of the final study. The data was used to aid in the sample size calculation. While it was highly suggestive of better pain control in the postoperative period for the patients that received the experimental drug combination, a formal, randomized trial was still necessary to evaluate the new regime.
2.4 PATIENT POPULATION

2.4.1 Inclusion Criteria

All patients undergoing primary augmentation mammoplasty at the Okanagan Plastic Surgery Centre who were candidates for a subpectoral implant were recruited for the study. Informed consent was obtained. The majority of these patients were from Kelowna and the surrounding area, but the catchment area included the entire Okanagan region.

2.4.2 Exclusion Criteria

Ethical considerations required that patients who might be harmed by either the principal or comparative exposures be excluded. Patients with allergies to Ketorolac, Bupivicaine, epinephrine or any of the medications set out in the anesthetic protocol were excluded. Patients undergoing augmentation mammoplasty that required a separate procedure at the same time (for example augmentation and co-incident mastopexy or breast lift) were excluded on scientific exclusion criteria in that they did not meet a strict operational definition of the condition being studied. Patients presenting for augmentation after previous augmentation (revision / secondary augment), correction of post-mastectomy defects or with any prior breast surgery were excluded on pragmatic criteria, as were those that refused to enter into the study.

2.5 STATISTICS

2.5.1 Statistical Analysis

A priori statistical analysis was used. For the purpose statistical analysis, it was necessary to identify only the control group (Group A). The other three groups were not identified until after the completion of the analysis therefore maintaining blinding. Only 95% confidence intervals were reported. The comparisons were non-orthogonal comparisons. The first statistical analysis performed used only the groups and the average VAPS data. Support at that level, that the patients in each group experienced a different level of pain, permitted the analysis to proceed further to incorporate other variables. An analysis of variance indicated whether the methods gave equal response, or whether one or more responses were different. After the analysis of variance was performed, it remained to determine whether the differences were statistically significant. This was done by performing one of a suite of tests referred to as "multiple comparison tests." The multiple comparison tests indicate (i) whether the differences are significant, (ii) the magnitude of the difference, and (iii) the direction of the difference.

2.5.2 Mathematics and Statistical Formulas

Recommendations about analysing data for the purpose of multiple comparisons were made by Hsu.\(^8\) "Specifically, for confidence intervals, if all pairwise comparisons are of primary interest, then Tukey’s method for balanced design and the Tukey-Kramer
method for unbalanced design are recommended. … If comparisons with a control are of primary interest, then Dunnett’s method is recommended."

2.5.3 Sample Size Estimation

There are four considerations in calculating a sample size. (1) desired level of significance, $\alpha$ (2) power (1-$\beta$) to detect an actual difference, $\mu_1$ (3) what difference must be detected between means ($\mu_1 - \mu_0$) and (4) an estimate of standard deviation, SD $\sigma$.

This sample size calculation is also based on the assumptions that the standard deviations and sample sizes are equal between the groups. Accepting an $\alpha$ of 0.05 and a $\beta$ of 90% and using a $\sigma$ of 1.0 and $\mu_1 - \mu_0$ of two and four respectively (from the pilot study) one can solve for the sample size $n$ in the following equation:

$$n = 4 \left( \frac{(Z_{\alpha})(Z_{\beta})(\sigma)}{(\mu_1 - \mu_0/\mu_0)} \right)$$

$$n = 4\left(\frac{(1.96)(1.28)(1.0)/(0.5)}\right]$$

$$n = 20.07 \text{ rounded to 21}$$

Therefore, 21 people were needed for each group, or a total of 84 people. To allow for dropouts and incomplete data, 25 people were entered for a total of 100 people total. A retrospective OR review indicated that to gather this many patients would require approximately eight months.

2.5.4. Statistical Formulas

Before performing the Tukey, Dunnett and Bonferroni methods, an analysis of variance was executed. The analysis of variance provided the mean square error (MSE) which is required for the multiple comparisons.

2.5.4.1 Tukey’s Method for all Pairwise Comparisons

Tukey’s method(81) provides simultaneous confidence intervals for all pairwise differences (of means). These confidence intervals, for all pairwise groups $i$ and $j$, are given by

$$\hat{\mu}_i - \hat{\mu}_j \pm q^* \sqrt{\frac{2}{n}}$$

for all $i \neq j$,

where $\hat{\mu}_i$ and $\hat{\mu}_j$ are the estimated means of groups $i$ and $j$ respectively, $q^*$ is the critical value, $\hat{\sigma}$ is the square root of the mean square error (MSE) obtained from the analysis of variance, and $n$ is the number of observations used in obtaining the means of the groups. In the pairwise differences case $n$ is determined as follows: there are 25 patients in each group, with four measurements each at the 0, 30, 60 minute and discharge times, so every group mean is based on $n = 100$ observations.
The critical value $q^*$ is given by the solution of the following equation:

$$P \left\{ \frac{\left| \hat{\mu}_i - \mu_i - \left( \hat{\mu}_j - \mu_j \right) \right|}{\sigma \sqrt{2/n}} \leq q^* \right\} = 1 - \alpha,$$

where $\mu_i$ and $\mu_j$ are the true population means for the $i$'th and $j$'th groups, and $\alpha$ is the level of probability being used in the construction of confidence intervals (0.05 in this case for a 95% confidence interval).

### 2.5.4.2 Bonferroni's Method for all Pairwise Comparisons

The critical value for Bonferroni’s method\(^{81}\) is given by

$$t = \left( \frac{2\alpha}{k(k-1)} \right)^{\frac{1}{2}},$$

where $t$ represents the Student’s $t$ statistic, at probability level $\frac{2\alpha}{k(k-1)}$, where $k$ is the number of groups, $\alpha$ is again the desired confidence level (0.05 for a 95% confidence interval), and $\nu$ represents the degrees of freedom (384). One reason for the closeness of the results between Tukey’s and Bonferroni’s methods is that the degrees of freedom are very high at 384.

### 2.5.4.3 Dunnett’s Method for Comparisons With a Control

The two-sided confidence interval, for comparing the specific groups (B, C and D in this case) with the control Group A (Dunnett’s method\(^{81}\)) is given by

$$\hat{\mu}_i - \hat{\mu}_k \pm d \cdot \sigma \sqrt{\nu_i^k}, \text{ for } i = 1, \ldots, k - 1,$$

where $k$ is the number of groups being compared, $\sigma^2 \nu_i^k$ is the variance of the difference in the estimators of the means, $\hat{\mu}_i - \hat{\mu}_k$. The constant $|d|$, (absolute value thereof) is given by the solution of the following equation

$$P \left\{ \max_{1 \leq i \leq k-1} \left| \frac{\hat{\mu}_i - \hat{\mu}_k - (\mu_i - \mu_k)}{\sigma \sqrt{\nu_i^k}} \right| \leq |d| \right\} = 1 - \alpha,$$

where the variables are defined above.
2.6 STUDY METHODOLOGY

This study was designed as a prospective, randomized, triple-blind clinical trial.

2.6.1 Ethical Approval

All surgical procedures as well as follow-up visits were performed at the private Okanagan Plastic Surgery Center. Ethical approval for this study was obtained from the Medical Director of this facility. The OPSC is also within the Okanagan / Similkameen Health Region. While no part of the study was to be carried out in a public facility, there could potentially have been occasion requiring a patient be transferred to the Kelowna General Hospital. Therefore ethical approval was also obtained from the Ethics Review Board of the Okanagan / Similkameen Health Region through the Kelowna General Hospital.

2.6.2 Randomization

There was no prognostic stratification. The randomization of patients was performed as follows. One hundred index cards, twenty-five for each group, were prepared with a label specifying the group (A, B, C and D). These index cards were then folded in half, covering the label, and placed in envelopes. The envelopes were then sealed. A random number generating program was used to randomly assign the numbers one through one hundred to the envelopes. Finally, they were placed in consecutive order. With this approach, baseline factors, such as age and pain threshold, were distributed randomly among the various study groups.

2.6.3 Triple-Blind

The one hundred, consecutively numbered envelopes were placed in the care of a nurse (RN-1) at the OPSC. Each week, this nurse checked the operating room slate for the upcoming week to identify days on which an augmentation mammoplasty had been booked. On the morning of each scheduled procedure, the nurse opened an envelope and prepared the appropriate mixtures in a syringe. The syringe was labeled with the patient’s name and the number from the envelope. The patient, anesthetist and surgeon were unaware as to the contents of the syringe. All four solutions were made up to the same volume and had similar appearances. At the time of surgery, the surgeon used the syringe to irrigate the solution into the pocket created for the implant. As the solution was irrigated into the wound and not injected subcutaneously, there was no superficial skin blanching from the epinephrine and hence no indication to the surgeon as to the solution used.

After the procedure, the patient was transferred to the recovery room. Care in the recovery room was administered by a separate nurse (RN-2) from the nurse that prepared the solution in the syringe. In this manner, the first nurse (RN-1) was the only person with a list of the patient names and groups to which they were assigned. For statistical analysis, the groups were identified only as groups A through D effectively blinding the
researcher. This constitutes a triple-blind study, the purpose of which is to eliminate as much bias as possible from the study.

2.6.4 Anesthetic Protocol

The goal of this study was to test the effectiveness of locally administered, intraoperative Ketorolac and Bupivicaine with epinephrine at reducing pain in the postoperative period. A possible confounding factor would have been the medications given as an anesthetic. To avert this complication, an anesthetic protocol was developed in consultation with the Head of Anesthesia at the Kelowna General Hospital and the Okanagan Plastic Surgery Center. The details of the protocol are listed in Table 3.

Table 3. Anesthetic Protocol

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Usual Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.03mg/kg</td>
<td>2mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2-3mcg/kg</td>
<td>150mcg</td>
</tr>
<tr>
<td>Propofol</td>
<td>2mg/kg</td>
<td>140mg</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.30mg/kg</td>
<td>25mg</td>
</tr>
<tr>
<td>Droperidol</td>
<td>0.01mg/kg</td>
<td>0.625mg</td>
</tr>
<tr>
<td>Forane</td>
<td>0.8-2%</td>
<td>titrated</td>
</tr>
</tbody>
</table>

Inhaled Gases 60% N\textsubscript{2}O and 40% O\textsubscript{2}

Reversal (if required)
- Neostigmine 2.0mg
- Glycopyrolate 0.4mg

Postoperative
- Morphine 2mg IV PRN
- Gravol 25mg IV PRN
- Tylenol #3 1-2 tabs PO PRN

At the time of this study, there were twelve active anaesthiologists working at both the Kelowna General Hospital and the Okanagan Plastic Surgery Center. The protocol was presented at a Department of Anesthesia general meeting at which all anaesthiologists were in attendance. The protocol was unanimously accepted and all agreed that it would be strictly adhered to for the study patients. The anaesthesia time started when the patient entered the operating theatre and ended when the patient was sufficiently able to maintain their own airway and was taken to the recovery room.
2.6.5 Operative Procedure

The same operative procedure was used on all patients. The surgery was performed by three plastic surgeons with at least 5 years of experience in breast augmentation. The implant sizes were marked on the patient's chart. Access to the surgical plane of dissection for the implant insertion was gained through a breast incision. A 3cm incision was used bilaterally. The incision was opened and was dissected inferiorly down to the chest wall. The dissection was then turned cephalad and the implant pocket was developed under the pectoralis major muscle. The dissection partially detached the sternal origins of the pectoralis major muscle below the third intercostal space. The costal origins of the pectoralis major muscle were also partially detached. Dissection was performed with electrocautery on coag mode with a blend 1 setting of 40. After developing the implant pocket, it was irrigated with saline and then a 50% Betadine solution and suctioned. The implant pocket was then irrigated with solution in the numbered syringe. The surgeon documented the difficulty of dissection. The study used three codes to distinguish the difficulty of dissection. The definition of these codes appears in Table 4.

Table 4. Coding to Establish Difficulty of Dissection

<table>
<thead>
<tr>
<th>Code</th>
<th>Dissection</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Easy</td>
<td>Minimal</td>
</tr>
<tr>
<td>2</td>
<td>Moderate; medial muscle insertions released</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Difficult; broad insertion with large musculature release</td>
<td>Significant; large perforators (increased cautery usage)</td>
</tr>
</tbody>
</table>

Prior to insertion, the saline inflatable implant of the desired size was inflated, checked for leaks and dipped in Betadine. The implant size was recorded. The implant was then inserted into the pocket, positioned and inflated to the desired fill volume with normal saline using a closed filling system. Once a satisfactory placement was established, a three layer closure was performed using 3-0 Vicryl for the two deep layers and a 4-0 Monocryl for the running intracuticular stitch. The OR time ended when the surgeon completed the final layer of closure. A sports brassiere was used as the final dressing.

2.6.6 Interventions

The intervention under study was the solution that was irrigated into the implant pocket after dissection and prior to implant insertion. Those solutions were prepared according to the guidelines set out in Table 5. The Ketorolac was supplied in two ml vials of 30 mg/ml solution. One half percent Bupivacaine with epinephrine was used. The solutions were stored in a 30cc syringe.
Table 5. Intervention Solution Compositions

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal Saline (ml)</th>
<th>Ketorolac (ml) 30mg/ml</th>
<th>0.5% Bupivacaine with epinephrine (ml)</th>
<th>Total Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>B</td>
<td>29</td>
<td>1</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>C</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>D</td>
<td>14</td>
<td>1</td>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

For each patient, the solution was irrigated into the implant pocket intraoperatively. Compliance and crossovers (patients that receive both treatments in the trial) were therefore not an issue. The patient’s analgesics were controlled by the operating room and recovery room staff. This effectively eliminated contamination (patients assigned to the control arm that subsequently undergo experimental intervention) and co-interventions (additional therapies made available to patients in any arm of the study). If however, one of these situations had arisen, the patient would have been analyzed in the group to which they were originally assigned. All withdrawals were to be documented along with their reason for departure.

2.6.7 Outcome Measures

As the intervention was directed at control of pain in the postoperative period, an accurate measure of the patient’s pain intensity was required. The outcome measure selected was the visual analog pain scale. For this study, a horizontal line of 10cm was employed. The points zero and 10 and the descriptions of “no pain” and “worst pain imaginable” were used as anchor points. No other descriptors were placed on the line.

RN-2 administering the VAPS was blinded to the patient’s group allocation. The VAPS was administered once the patient was lucid in the immediate postoperative period, at one half hour, one hour and at the time of discharge. The type and dose of rescue medications given were recorded.

The secondary outcome measure was the time spent in the recovery room. This was recorded as the time that the patient arrived in the recovery room until the time that patient no longer required the services of the recovery room as decided by the anaesthesiologist and nurse (RN-2).

Other data collected at the time of surgery included patient demographics, implant size (both left and right), implant fill (left and right), anesthesiologist, anesthesia time, OR time, dissection code and PAR time. A copy of the complete data collection form is located in Appendix B.
CHAPTER 3: RESULTS AND DATA ANALYSIS

3.1 EXPLORATORY DATA ANALYSIS

The groups A, B, C, and D were normal saline, Ketorolac only, Bupivicaine only and Ketorolac and Bupivicaine respectively. Exploratory data analysis consisted of graphing the VAPS data as a function of time for each group separately, as shown in Figure 1. Each circle represented a VAPS measurement at that time. Time from the first assessment, in minutes, was measured along the lower axis in each graph. The VAPS data was represented by the vertical axis. The data points were slightly jittered so the points did not lie one on top of another, to highlight regions of higher density. There was a difference between Group A and the three other groups. For Group A there is a clustering (or greater density) of high VAPS values for the 0, 30 and 60 minute values. In Group B the highest density clustering of VAPS values occurred at four or less. In Group C the highest density clustering occurred at three or less. In Group D the clustering occurred at VAPS values of one or less.

The exploratory data analysis revealed that Groups C and D had the least amount of postoperative pain, closely followed by B. The pain assessed by the Group A patients appeared to be very different from the other three groups and far greater because the VAPS values were so high compared to the other groups of patients.
3.2 ANALYSIS OF VARIANCE

Table 6 displays the results of the analysis of variance. This was performed to determine the mean square error. There is a highly significant difference in the pain results between the groups. The F-value for methods is very large at 33.01 with the associated probability of $F = 0.000$. This indicates that the mean VAPS values for the methods differ significantly.

<table>
<thead>
<tr>
<th></th>
<th>Df</th>
<th>Sum of Sq</th>
<th>MSE</th>
<th>F Value</th>
<th>Pr(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>3</td>
<td>62.003</td>
<td>20.6678</td>
<td>3.99524</td>
<td>0.0050341</td>
</tr>
<tr>
<td>Methods</td>
<td>3</td>
<td>512.401</td>
<td>170.8005</td>
<td>33.01698</td>
<td>0.0000000</td>
</tr>
<tr>
<td>Time:Methods</td>
<td>9</td>
<td>42.689</td>
<td>4.7433</td>
<td>0.91691</td>
<td>0.5102650</td>
</tr>
<tr>
<td>Residuals</td>
<td>384</td>
<td>1986.474</td>
<td>5.1731</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.3 PRIMARY OUTCOME

Significance in the following tables is represented by "****" and was determined with 95% confidence intervals.

3.3.1 All Pairwise Comparisons

3.3.1.1 Tukey Method

In Table 7, all pairwise comparisons of the mean VAPS values are presented. The label A-B implies the mean of Group A minus the mean of Group B. Group A, had an average pain level of 4.15 units. This was 1.59 units greater than Group B, 2.50 units greater than Group C and 2.96 units greater than Group D. Group B had an average pain level 0.911 units greater than Group C and 1.38 units greater than group D. All of these differences between mean pain levels were significant. Group C had an average pain level 0.464 units greater than Group D, but the confidence interval included zero indicating no statistical significance. These results are represented graphically in Figure 2.

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-B</td>
<td>1.590</td>
<td>0.322</td>
<td>0.759</td>
<td>2.42</td>
<td>****</td>
</tr>
<tr>
<td>A-C</td>
<td>2.500</td>
<td>0.322</td>
<td>1.670</td>
<td>3.33</td>
<td>****</td>
</tr>
<tr>
<td>A-D</td>
<td>2.960</td>
<td>0.322</td>
<td>2.130</td>
<td>3.79</td>
<td>****</td>
</tr>
<tr>
<td>B-C</td>
<td>0.911</td>
<td>0.322</td>
<td>0.081</td>
<td>1.74</td>
<td>****</td>
</tr>
<tr>
<td>B-D</td>
<td>1.380</td>
<td>0.322</td>
<td>0.545</td>
<td>2.20</td>
<td>****</td>
</tr>
<tr>
<td>C-D</td>
<td>0.464</td>
<td>0.322</td>
<td>-0.366</td>
<td>1.29</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2. All Pairwise Comparisons.

3.3.1.2 Bonferroni Method

In Table 8, the pairwise differences are shown using the Bonferroni’s method. The Bonferroni and Tukey results are identical to the second decimal place. They are shown only for completeness and graphical representation was not done.

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-B</td>
<td>1.590</td>
<td>0.322</td>
<td>0.736</td>
<td>2.44</td>
<td>****</td>
</tr>
<tr>
<td>A-C</td>
<td>2.500</td>
<td>0.322</td>
<td>1.650</td>
<td>3.35</td>
<td>****</td>
</tr>
<tr>
<td>A-D</td>
<td>2.960</td>
<td>0.322</td>
<td>2.110</td>
<td>3.82</td>
<td>****</td>
</tr>
<tr>
<td>B-C</td>
<td>0.911</td>
<td>0.322</td>
<td>0.058</td>
<td>1.76</td>
<td>****</td>
</tr>
<tr>
<td>B-D</td>
<td>1.380</td>
<td>0.322</td>
<td>0.522</td>
<td>2.23</td>
<td>****</td>
</tr>
<tr>
<td>C-D</td>
<td>0.464</td>
<td>0.322</td>
<td>-0.389</td>
<td>1.32</td>
<td></td>
</tr>
</tbody>
</table>

3.3.2 Comparisons with Control Group A

3.3.2.1 Dunnett’s Method

In Table 9, Groups B, C and D are compared with the control Group A using Dunnett’s test. Again the differences are shown as functions of subtractions of the mean values. As the output is given in alphabetical order, the differences are calculated as “B minus A,” and so on. Therefore, there is a minus sign in the difference of means column. On average, the experimental groups B, C and D experienced 1.5, 2.5 and 3.0 units less respectively than the Control group. All of the differences are significant demonstrating
that Groups B, C and D differ significantly from the control Group A. The results of the Dunnett statistical analysis are represented graphically in Figure 3.

Table 9. Comparisons with Control Group Using Dunnett’s Method

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-A</td>
<td>-1.59</td>
<td>0.322</td>
<td>-2.35</td>
<td>-0.83</td>
<td>****</td>
</tr>
<tr>
<td>C-A</td>
<td>-2.50</td>
<td>0.322</td>
<td>-3.26</td>
<td>-1.74</td>
<td>****</td>
</tr>
<tr>
<td>D-A</td>
<td>-2.96</td>
<td>0.322</td>
<td>-3.72</td>
<td>-2.21</td>
<td>****</td>
</tr>
</tbody>
</table>

Figure 3. Comparisons with the Control Group A.

3.3.2.2 Bonferroni’s Method

For completeness, the comparisons with the control Group A are shown using Bonferroni’s method in Table 10. The results agree to the first decimal place with Dunnett’s method and again are not represented graphically.

Table 10. Comparisons with Control Group Using Bonferroni’s Method

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-A</td>
<td>-1.59</td>
<td>0.322</td>
<td>-2.36</td>
<td>-0.816</td>
<td>****</td>
</tr>
<tr>
<td>C-A</td>
<td>-2.50</td>
<td>0.322</td>
<td>-3.27</td>
<td>-1.730</td>
<td>****</td>
</tr>
<tr>
<td>D-A</td>
<td>-2.96</td>
<td>0.322</td>
<td>-3.74</td>
<td>-2.190</td>
<td>****</td>
</tr>
</tbody>
</table>
3.4 PRIMARY OUTCOME ANALYSIS BY TIME PERIOD

All patients spent at least 90 minutes in the recovery room. Individual discharge times varied. In Figure 4, the average pain of the 25 patients in each group, with 95% confidence intervals, is shown for times 0, 30, 60 and discharge. The discharge data is shown attached to the 60 minute value by a dashed line to highlight the fact that the discharge times were random and patient dependent.

Figure 4. Visual Analog Pain Scale Averages and 95% Confidence Intervals for Average Pain as a Function of Time.

Group A had the most pain for all time periods. Average VAPS values decreased in order for Groups B, C and D. Group D always had the lowest pain values as a function of time. The 95% confidence intervals for Groups C and D overlapped at each of the four time intervals. In other words, there was no significant difference between the two groups.

3.4.1 Analysis of Variance by Time Period

The analysis of variance for each of the four time periods is presented in Table 11. For each time period, the Tukey and Dunnett analyses are presented. The standard error for
the multiple comparisons was obtained by multiplying the residual mean square error by
two and dividing by n, where n is the number of observations used to compute the
average for each group, and taking the square root. In this experiment, n was 25.

Table 11. Analysis of Variance for each Time Period

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Sum of Sq</th>
<th>MSE</th>
<th>F Value</th>
<th>Pr(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Op</td>
<td>129.428</td>
<td>43.1425</td>
<td>6.82995</td>
<td>3.204214e-4</td>
</tr>
<tr>
<td>30 min</td>
<td>165.022</td>
<td>55.0073</td>
<td>8.01398</td>
<td>8.035821e-5</td>
</tr>
<tr>
<td>60 min</td>
<td>182.523</td>
<td>60.8409</td>
<td>12.5405</td>
<td>5.483831e-7</td>
</tr>
<tr>
<td>Discharge</td>
<td>78.119</td>
<td>26.0396</td>
<td>9.78821</td>
<td>1.075773e-5</td>
</tr>
</tbody>
</table>

3.4.2 Postoperative (Time Zero)

The average VAPS values at time zero were 3.76, 1.4, 1.24 and 0.88 units for Groups A, B, C and D respectively. The Tukey multiple comparison test result is shown in Table 12

Table 12. Comparison of Pain at Entry to the Recovery Room

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-B</td>
<td>2.38</td>
<td>0.7111</td>
<td>0.521</td>
</tr>
<tr>
<td>A-C</td>
<td>2.52</td>
<td>0.7111</td>
<td>0.661</td>
</tr>
<tr>
<td>A-D</td>
<td>2.88</td>
<td>0.7111</td>
<td>1.020</td>
</tr>
<tr>
<td>B-C</td>
<td>0.14</td>
<td>0.7111</td>
<td>-1.720</td>
</tr>
<tr>
<td>B-D</td>
<td>0.50</td>
<td>0.7111</td>
<td>-1.360</td>
</tr>
<tr>
<td>C-D</td>
<td>0.36</td>
<td>0.7111</td>
<td>-1.500</td>
</tr>
</tbody>
</table>
Figure 5 Average Differences and 95% Confidence Intervals for All Pairwise Comparisons of Pain at Entry to the Recovery Room.

The result of the Dunnnett method of comparison for time zero is shown in Table 13 and represented graphically in Figure 6. Groups B, C and D had significantly less pain than Group A at time zero.

Table 13. Comparison with Control Group at Time Zero

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-A</td>
<td>-2.38</td>
<td>0.711</td>
<td>-4.08</td>
<td>-0.683 ****</td>
</tr>
<tr>
<td>C-A</td>
<td>-2.52</td>
<td>0.711</td>
<td>-4.22</td>
<td>-0.823 ****</td>
</tr>
<tr>
<td>D-A</td>
<td>-2.88</td>
<td>0.711</td>
<td>-4.58</td>
<td>-1.180 ****</td>
</tr>
</tbody>
</table>

Figure 6 Dunnnett Test Results Showing All Comparisons with the Control at Time Zero.
3.4.3 30 Minutes

After 30 minutes in the recovery room, average VAPS values were 4.68, 2.56, 1.76 and 1.36 units for the four groups in order. The Tukey multiple comparison test result is shown in Table 14 and represented graphically in Figure 7. All differences with respect to Group A are significant at this time. Groups B, C and D showed no significant differences in average pain at 30 minutes.

Table 14. Comparison of Pain at 30 Minutes

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-B</td>
<td>2.120</td>
<td>0.741</td>
<td>0.187</td>
<td>4.06</td>
</tr>
<tr>
<td>A-C</td>
<td>2.930</td>
<td>0.741</td>
<td>0.995</td>
<td>4.87</td>
</tr>
<tr>
<td>A-D</td>
<td>3.320</td>
<td>0.741</td>
<td>1.390</td>
<td>5.26</td>
</tr>
<tr>
<td>B-C</td>
<td>0.808</td>
<td>0.741</td>
<td>-1.130</td>
<td>2.75</td>
</tr>
<tr>
<td>B-D</td>
<td>1.200</td>
<td>0.741</td>
<td>-1.737</td>
<td>3.14</td>
</tr>
<tr>
<td>C-D</td>
<td>0.392</td>
<td>0.741</td>
<td>-1.550</td>
<td>2.33</td>
</tr>
</tbody>
</table>

Figure 7 Average Difference and 95% Confidence Intervals for All Pairwise Comparisons of Pain at 30 Minutes After Entry to the Recovery Room.

Figure 8 shows the result of the Dunnett method of comparison at 30 minutes postop, with Groups B, C and D having significantly less pain than Group A at 30 minutes.
Table 15. Comparison with Control Group at 30 Minutes

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-A</td>
<td>-2.12</td>
<td>0.741</td>
<td>-3.89</td>
<td>-0.355</td>
</tr>
<tr>
<td>C-A</td>
<td>-2.93</td>
<td>0.741</td>
<td>-4.70</td>
<td>-1.160</td>
</tr>
<tr>
<td>D-A</td>
<td>-3.32</td>
<td>0.741</td>
<td>-5.09</td>
<td>-1.560</td>
</tr>
</tbody>
</table>

Figure 8 Dunnet Test Results Showing All Comparisons with the Control at 30 Minutes.

3.4.4 One Hour

At the one hour point, the average VAPS values were 4.80, 3.52, 1.8, and 1.44 units for Groups A, B, C and D respectively. The Tukey multiple comparison test result is shown in Table 16 and represented graphically in Figure 9. Groups A and B were not significantly different at one hour. Groups C and D had significantly less pain than Groups A and B, but there was again no difference between the pain experienced by Groups C and D at one hour postoperative.

Table 16. Comparison of Pain at One Hour

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-B</td>
<td>1.280</td>
<td>0.623</td>
<td>-0.3490</td>
<td>2.91</td>
</tr>
<tr>
<td>A-C</td>
<td>2.980</td>
<td>0.623</td>
<td>1.3600</td>
<td>4.61</td>
</tr>
<tr>
<td>A-D</td>
<td>3.360</td>
<td>0.623</td>
<td>1.7300</td>
<td>4.99</td>
</tr>
<tr>
<td>B-C</td>
<td>1.700</td>
<td>0.623</td>
<td>0.0751</td>
<td>3.33</td>
</tr>
<tr>
<td>B-D</td>
<td>2.080</td>
<td>0.623</td>
<td>0.4510</td>
<td>3.71</td>
</tr>
<tr>
<td>C-D</td>
<td>0.376</td>
<td>0.623</td>
<td>-1.2500</td>
<td>2.00</td>
</tr>
</tbody>
</table>
Figure 9 Average Difference and 95% Confidence Intervals for All Pairwise Comparisons of Pain at 60 Minutes After Entry to the Recovery Room.

The result of the Dunnett method of comparison at one hour is shown in Table 17 and represented graphically in Figure 10. As with Tukey’s method, Dunnett’s method demonstrated no significant difference between Groups A and B one hour postoperative. Groups C and D were significantly different from Group A.

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-A</td>
<td>-1.28</td>
<td>0.623</td>
<td>-2.77</td>
<td>0.207</td>
</tr>
<tr>
<td>C-A</td>
<td>-2.98</td>
<td>0.623</td>
<td>-4.47</td>
<td>-1.500</td>
</tr>
<tr>
<td>D-A</td>
<td>-3.36</td>
<td>0.623</td>
<td>-4.85</td>
<td>-1.870</td>
</tr>
</tbody>
</table>
Figure 10 Dunnet Test Results Showing All Comparisons with the Control at 60 Minutes.

![Dunnet Test Results Graph](image)

Differences of Visual Analog Scale Values for Sixty Minutes Time
(Bullets Represent Average Differences)
Simultaneous 95 % Confidence Limits, Dunnett Method

3.5.4 Discharge

At the time of discharge from the recovery room, Groups A, B, C and D reported average VAPS values of 3.36, 2.80, 1.80 and 1.08 respectively. The Tukey multiple comparison test result is shown in Table 18 and represented graphically in Figure 11. Groups A and B did not have a significant difference in average pain at discharge. Group A had significant pain difference compared to Groups C and D. Group B was not significantly different from Group C but it was different compared with Group D. Group C and D were not significantly different at discharge.

Table 18. Comparison of Pain at Discharge

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-B</td>
<td>0.572</td>
<td>0.461</td>
<td>-0.634</td>
<td>1.78</td>
</tr>
<tr>
<td>A-C</td>
<td>1.560</td>
<td>0.461</td>
<td>0.358</td>
<td>2.77</td>
</tr>
<tr>
<td>A-D</td>
<td>2.290</td>
<td>0.461</td>
<td>1.090</td>
<td>3.50</td>
</tr>
<tr>
<td>B-C</td>
<td>0.992</td>
<td>0.461</td>
<td>-0.214</td>
<td>2.20</td>
</tr>
<tr>
<td>B-D</td>
<td>1.720</td>
<td>0.461</td>
<td>0.514</td>
<td>2.93</td>
</tr>
<tr>
<td>C-D</td>
<td>0.728</td>
<td>0.461</td>
<td>-0.478</td>
<td>1.93</td>
</tr>
</tbody>
</table>

**** indicates significant difference.
Figure 11 Average Difference and 95% Confidence Intervals for All Pairwise Comparisons of Pain at Discharge.

The result of the Dunnett method of comparison at discharge is shown in Table 19 and represented graphically in Figure 12. As with Tukey’s method, Dunnett’s method demonstrated no significant difference between Groups A and B at the time of discharge. Groups C and D were significantly different from Group A.

Table 19. Comparison with Control Group at Discharge

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-A</td>
<td>-0.572</td>
<td>0.461</td>
<td>-1.67</td>
<td>0.529</td>
</tr>
<tr>
<td>C-A</td>
<td>-1.560</td>
<td>0.461</td>
<td>-2.67</td>
<td>-0.463</td>
</tr>
<tr>
<td>D-A</td>
<td>-2.290</td>
<td>0.461</td>
<td>-3.39</td>
<td>-1.190</td>
</tr>
</tbody>
</table>

Figure 12 Dunnet Test Results Showing All Comparisons with the Control at Discharge.
3.6 SECONDARY OUTCOME AND OTHER VARIABLES

Exploratory data analysis was performed on the other variables. These are descriptive statistics only and are represented graphically. No statistical analysis was performed. The data is summarized in Table 20.

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Ketorolac</th>
<th>Bupivicaine</th>
<th>Ketorolac and Bupivicaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postop</td>
<td>3.76</td>
<td>1.40</td>
<td>1.24</td>
<td>0.88</td>
</tr>
<tr>
<td>30 min</td>
<td>4.68</td>
<td>2.56</td>
<td>1.76</td>
<td>1.36</td>
</tr>
<tr>
<td>1 hr</td>
<td>4.80</td>
<td>3.52</td>
<td>1.80</td>
<td>1.44</td>
</tr>
<tr>
<td>D/C</td>
<td>3.36</td>
<td>2.80</td>
<td>1.80</td>
<td>1.08</td>
</tr>
<tr>
<td>Avg. Dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>1.8</td>
<td>2.0</td>
<td>1.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Avg. Volume (cc)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>401.4</td>
<td>382.2</td>
<td>375.7</td>
<td>397.2</td>
</tr>
<tr>
<td>Right</td>
<td>402.0</td>
<td>381.2</td>
<td>380.6</td>
<td>398.0</td>
</tr>
<tr>
<td>Time (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>93.9</td>
<td>86.3</td>
<td>89.3</td>
<td>94.3</td>
</tr>
<tr>
<td>OR</td>
<td>65.3</td>
<td>56.8</td>
<td>60.4</td>
<td>62.0</td>
</tr>
<tr>
<td>PAR</td>
<td>161.1</td>
<td>157.6</td>
<td>171.6</td>
<td>148.0</td>
</tr>
<tr>
<td>Narcotic Use*</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Postop Nausea*</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Anti-Emetic*</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*Numbers indicate ranking; 1 being the worst and 4 the best.
All 12 of the active anaesthesiologists took part in the study. On average, they performed the anaesthesia for eight patients. The plot of discharge pain versus anaesthesiologist, Figure 13, appeared to relate more towards the group rather than the anaesthesiologist. In general, the average pain was flat as a function of anaesthesiologist.

Figure 13. Average pain vs. anaesthesiologist.
The average anaesthesia time was 90.1 minutes with a range of 60 to 164 minutes. The second longest anaesthesia time was 120 minutes. The average anaesthesia times in minutes for Groups A, B, C and D were 93.9, 86.3, 89.3 and 94.3 respectively. A plot of average pain as a function of group and anaesthesia time appeared to relate more to the group than the anaesthesia time. This is seen in Figure 14. For a given group, the correlation between average pain and anaesthesia time appeared to be close to zero.

Figure 14. Average pain as a function of group and anaesthesia time.
The average OR time was 61.1 minutes with a range of 40 to 140 minutes. The second longest OR time was 95 minutes. The average Group OR times in minutes were 65.3 for A, 56.8 for B, 60.4 for C and 62.0 for D. A plot of average pain as a function of group and OR time appeared to relate more to the group than the OR time. This is seen in Figure 15. For a given group, the correlation between average pain and OR time appeared to be close to zero.

Figure 15. Average pain as a function of group and OR time.
The difference between anaesthesia time and OR time averaged 30 minutes for the 100 patients. The range for the average difference in anaesthesia time and OR time was 29 to 32 minutes.

The dissection codes, as reported by the surgeon, were 17, 81 and 2 for codes 1, 2 and 3 respectively for an average dissection code of 1.85. Of the cases reported as a code 1, six were from Group A, one from Group B, six from Group C and four from Group D. The two cases reported as code three were both in Group D. There did not appear to be enough difference between the three codes to indicate an effect. Average pain versus dissection code is plotted in Figure 16.

Figure 16. Average pain as a function of dissection code.
The average left implant size was 349.4 cc and on average was filled to 388.6 cc with a fill range of 250 to 700 cc. The average right implant size was 349.7 cc and on average was filled to 390.4 cc with a fill range of again 250 to 700 cc. The most frequent implant was a 300 cc Mentor model 1600 round saline implant. The average left implant volumes were 401, 382, 376 and 397 cc for in order for groups A through D. On the right, the average implant volumes were 402, 381, 381 and 398 again in order. Average pain was plotted as a function of implant fill volume. In general, the results supported Group having more of an effect on average pain than implant fill volume. In Groups B and D however, there may have been a small dependence of average pain on volume. As implant fill volumes were similar from left to right, only the plot of average pain versus right implant fill size is given in Figure 17.

Figure 17. Plot of average pain as a function of right implant fill volume.
The average PAR time was 159.6 minutes with a range of 90 to 390 minutes. The average PAR time by group was 161.1, 157.6, 171.6 and 148.0 minutes for Groups A, B, C and D respectively. The percentage difference in PAR time between the four groups was small. Figure 18 shows an analysis of the average pain level reported by the different groups and the average time of leaving the recovery room. Groups B and C each had one “outlier” value of greater than 300 minutes. Figure 19 shows the means excluding the two outlier values. As seen before, average pain decreased as a function of group. With the outlier values excluded, it appears that Groups B and D are similar and Groups A and C are similar in discharge times.

Figure 18. Average Pain at Discharge, with 95% Confidence Interval, vs. Average PAR Time, with 95% Confidence Interval, All Patients Included.
Figure 19 Average Pain at Discharge, with 95% Confidence Interval, vs. Average PAR Time, with 95% Confidence Interval, One Patient over 300 minutes removed from Each of Group B and Group C.
CHAPTER 4: DISCUSSION

4.1 EVALUATION OF HYPOTHESIS

The findings of this study allow rejection of the null hypothesis and support the alternate hypothesis that in women undergoing primary augmentation mammaplasty, intraoperative Ketorolac combined with Bupivicaine with epinephrine irrigated into the surgical wound reduced pain in the immediate postoperative period. The power of this study was 0.90 and 95% confidence intervals were used to determine significance.

The group that was irrigated with normal saline only had the most pain in the postoperative period (4.15 units). The groups that were irrigated with Ketorolac only, Bupivicaine only and Ketorolac and Bupivicaine had less pain, on average (2.57, 1.65 and 1.19 units respectively). The multiple comparisons tests showed that irrigation with Ketorolac and Bupivicaine resulted in significantly less pain than irrigation with saline or Ketorolac alone. While there is some evidence that irrigation with Ketorolac and Bupivicaine resulted in less pain, on average, than irrigation with Bupivicaine alone, the evidence was not great enough to show a significant statistical difference as the confidence interval of the difference in average pain level included zero.

This study showed the effectiveness of locally administered, intraoperative Ketorolac and Bupivicaine with epinephrine at reducing pain in the first two-hours of the postoperative period. While the study was designed to compare normal saline with Ketorolac and Bupivicaine, the Ketorolac only and Bupivicaine only groups do provide other insightful information.

4.2 CONSIDERATION OF OTHER VARIABLES

Data was collected on a number of other variables at the time of the study. Descriptive statistics were applied to this data as shown in the results section.

4.2.1 Anaesthesia

In order to minimize the potential confounding factor of anaesthesia, an anaesthetic protocol was developed. All 12 anaesthesiologists reported that they were able to function within and adhere to the protocol for the duration of the study. Exploratory data analysis demonstrated that average pain was flat as a function of anaesthesiologist and related more to group. The anaesthesia time started when the patient entered the operating room. The anaesthesiologist would then start intravenous lines, connect monitoring devices and induce a general anaesthesia. At the end of the operation, the anaesthesiologist was then responsible for reversing the anaesthesia. The anaesthesia time ended when the patient was sufficiently able to maintain their own airway and was taken to the recovery room. The average anaesthesia time did not vary widely for the four groups (range 86 to 94 minutes). The correlation between average pain and anaesthesia time also appeared to be close to zero. The difference between anaesthesia
time and OR time again suggested that all patients were treated similarly regardless of anaesthesiologist.

Much of the rationale for the Ketorolac Bupivicaine solution was examined in the introduction. One aspect that deserved more attention was the rationale for getting away from postoperative pain control with opioids. The most widely recognized problems with opioid analgesia is the correlation with postoperative nausea and vomiting, excessive sedation and disorientation to time and place.\(^{(82)}\) The decided advantage of Ketorolac over opioids is the absence of nausea and vomiting in the intraoperative and postoperative period.\(^{(83)}\) A more recently recognized difficulty with opioid analgesia was documented by Célèrier et al.\(^{(84)}\) In that study, opioids produced acute analgesia to a noxious stimulus that lasted a few hours. However, after that time, the rats developed hyperalgesia that lasted for days. The researchers proposed that the opioids were activating N-methyl-D-aspartate pain facilitatory processes, which actually oppose analgesia and lead to long-lasting enhancement in pain sensitivity. It remains to be seen if this effect is also seen in humans.

### 4.2.2 Surgeon and Operation

The three surgeons performed 100 operations and reported using the same operative procedure described in the methods section for all patients. The OR time started when the surgeon made the first incision. The dissection code was determined just prior to the final implant insertion. The majority of the dissection codes were reported as average difficulty (code 2). Dissection code did not appear to have an effect on average pain. The OR time ended when the surgeon completed the final layer of closure. Average OR times ranged from 57 to 65 minutes for the four groups and the correlation between OR time and average pain appeared to be very small. The dissection of the implant pocket constitutes the most time consuming part of the operation and a longer OR time was most often due to a longer dissection. Since the solution was not irrigated into the pocket until after the dissection was complete, this may explain the possible slight correlation between average pain and OR time. The extra time before the solution is irrigated gives the pain more time to become entrenched. It would however, be difficult to circumvent this problem.

The timing of the irrigation of the solution was judiciously selected. Pre-incisional local anaesthetic infiltrations have been shown to be more effective in reducing postoperative pain and/or analgesic requirements than postincisional\(^{(16)}\) or post-surgical\(^{(85)}\) administration of the same agent by the same route. However, the preoperative administration of Ketorolac is relatively contraindicated in breast augmentation due to its effects on platelets and the increased risk of bleeding. If the risk of bleeding was insignificant, as in smaller procedures, then the NSAID could be given preoperatively. Using Tenoxicam, this was shown to improve postoperative analgesia in patients undergoing breast biopsy.\(^{(42)}\)
4.2.3 Implant Size

During the design phase of this study, several surgeons were consulted. Most anecdotally felt that the implant size would not have an impact on postoperative pain except in the case of exceedingly large implants. Overall, the exploratory data analysis demonstrated no apparent effect of implant fill volume on average pain. The Ketorolac only and the Ketorolac and Bupivicaine groups may have shown a very small dependence of average pain on implant fill volume, but this was not definite. The average implant sizes were the same for all four groups of patients. In 87 of the 100 cases, there was no difference from left to right. In the 13 cases with asymmetry, the difference was never greater than 50 cubic centimetres. As it is common for women’s breast to be slightly asymmetrical, this is not an unexpected finding. The largest implants were 625 cc implants filled to 700 cc bilaterally in a patient that received normal saline only. Interestingly, this patient reported pain scores of zero, one, six and one for the postop, 30 minute, 60 minute and discharge time intervals respectively. She did require four milligrams of morphine in the recovery room to help control her discomfort, but her pain scores and narcotic use were less than that of several of her counterparts in the normal saline only group.

4.3 PAIRWISE COMPARISONS AND COMPARISON WITH CONTROLS

4.3.1 Postoperative (Time Zero)

When the operation was complete, the anaesthesiologist proceeded to wake the patient. At the point that the anaesthesiologist felt that the patient was sufficiently awake to protect her own airway, the patient was taken to the recovery room. The first VAPS value was collected by the nurse once the patient was lucid enough to complete the task. The group irrigated with normal saline reported the highest average pain. The three other groups had significantly less pain, but differences between the experimental groups were not statistically significant.

Interestingly, irrespective of group membership, the patients had lower pain levels upon entry into the recovery room than 30 minutes later. There are still gaps in our knowledge of the actions of general anaesthetics. The mechanism of action has not yet been elucidated and as a result, accurate predictions or assessments of their duration of action are difficult. It was possible that the explanation for the lower VAPS values is that the patients were still under the influence of the general anaesthetics.

4.3.2 30 Minutes

After 30 minutes in the recovery room, average pain levels increased for all groups of patients. The cause of this effect is likely multifactorial. As discussed in the previous section, the duration of action of the general anaesthesia is uncertain. It would appear however, that the effects were beginning to diminish. Also, despite considerable attention to hemostasis during the operation, there would still be some expected bleeding into the operative field. In addition to these factors, there would be the immediate postop swelling and inflammation that is commonly seen after any operation.
The group irrigated with normal saline reported the highest average pain. The three other groups had significantly less pain, but differences between the experimental groups were again not statistically significant.

4.3.3 One Hour

After 60 minutes in the recovery room, all four groups reported their highest average pain levels. For the saline, Bupivicaine only and Ketorolac and Bupivicaine groups, there was only a slight increase from the 30 minute values. However, for the Ketorolac alone group, the average pain continued to rise sharply. At that point, there was not a significant difference between the pain experienced by the saline and the Ketorolac only groups. The Bupivicaine only and Ketorolac and Bupivicaine groups had, on average, less pain than both the saline and Ketorolac only groups. However, the Bupivicaine and the Ketorolac and Bupivicaine groups were not significantly different.

4.3.4 Discharge

While each patient spent at least 90 minutes in the recovery room, the individual times were quite varied. Therefore, the VAPS values at discharge represented pain assessments from different time periods. That is, for one patient the discharge VAPS value would have been collected 90 minutes after the completion of the operation while for a second patient, it may have been collected 150 minutes after the operation. The relative significance of this comparison is therefore questionable. Also, at that time, 23 of the saline only, 15 of the Ketorolac only, 14 of the Bupivicaine only and six of the Ketorolac and Bupivicaine patients had received some form of narcotics.

The average discharge pain value for the saline only group decreased to below the postop level. For the Ketorolac only group, the value decreased but was intermediate between the 30 and 60 minute value. In the Bupivicaine only group, the average discharge pain was the same as the 60 minute value and only 0.04 units higher than the 30 minute pain level. However, the 95% confidence intervals were decreasing, showing less scatter as time progressed. The average discharge pain value for the Ketorolac and Bupivicaine group decreased from the 60 minute level to an intermediate value between the postop and 30 minute value. At these values, the Bupivicaine only and Ketorolac and Bupivicaine groups were significantly better than the saline only group while the Ketorolac only group was not. The Ketorolac and Bupivicaine group was significantly better than the Ketorolac only group but the Bupivicaine only group was not. The Ketorolac and Bupivicaine group and the Bupivicaine only group once again did not differ significantly.

4.4 INTERPRETATION OF DIFFERENT GROUPS

4.4.1 Normal Saline

This group represented the current standard of care. Patients irrigated with normal saline reported the highest VAPS values at each time interval. Their reported pain was
significantly higher than the other groups at all time interval with the exception of the Ketorolac only at the one hour and discharge time intervals. This group of patients requested narcotic analgesics earlier, consumed the most narcotics in the recovery room (92mg of morphine, 200 µg of fentanyl, 710 mg of codeine and 155 mg of demerol), reported the highest rate of postop nausea (12 patients), correspondingly received more anti-nausea medications and had the second longest average PAR time. As narcotic analgesics are often nauseating, anti-nausea medications are frequently given at the same time and this must be taken into account.

4.4.2 Ketorolac Only

In the Ketorolac only group, the average pain immediately postop and at the 30 minute interval was significantly lower than the normal saline group. Therefore, it appeared that intraoperative irrigation with Ketorolac had some effect on postop pain. The effect has been attributed to an attenuated inflammatory response that reduces peripheral sensitization and its effects on the spinal nociceptive processing, including the induction and maintenance of central sensitization. However, at the 60 minute interval, this difference between the two groups was no longer present. By that time many of the patients in the saline group had received narcotics thereby lowering their pain levels. However, that factor alone was not enough to make the saline group similar to the Bupivicaine only group or the Ketorolac and Bupivicaine group so there must be other factors in conjunction with it.

One of the criticisms of Ketorolac as an analgesic is its inability to provide complete analgesia. This may have been a factor in the current study. The half-life of Ketorolac is 5.7 hours when administered intramuscularly or orally. However, its half-life when administered locally has not been documented. To abate this, it is possible to consider a higher dose of the NSAID. However, there is good evidence that a higher dose of Ketorolac either IM or orally is not more effective than the recommended dose and in fact has significantly greater risks.

The Ketorolac only group used the second highest volume of narcotics, reported the second highest postop nausea rate, received the second highest volume of anti-nausea medications but spent the second lowest average time in PAR.

IM and oral Ketorolac are contraindicated in the preoperative and intraoperative period when there is a risk of bleeding due to its affect on platelet function. No postop hematomas were noted with the locally applied Ketorolac or in any other group for that matter.

4.4.3 Bupivicaine Only

In the Bupivicaine only group, the average pain level was significantly lower than the normal saline group at all time intervals. This demonstrated an improvement in the control of postop pain over the current standard of care. Immediately postop and at the one hour interval, the Bupivicaine only group reported lower average VAPS values than
did the Ketorolac only group. At the 30 minute time interval and at the time of discharge, this difference was not significant. There was however, an overall significant difference. When compared with the Ketorolac and Bupivicaine group, the Bupivicaine only group was not significantly different.

This study was not designed to detect a difference between the Bupivicaine and Ketorolac with Bupivicaine groups. However, the data from this study could be used as pilot data for a further study. In that study, the null hypothesis would be that in women undergoing primary augmentation mammaplasty, there is no difference in postoperative pain between Ketorolac combined with Bupivicaine with epinephrine and Bupivicaine with epinephrine alone when irrigated into the surgical wound intraoperatively. The sample size for that study would be significantly greater than the current study as the difference in means is smaller. Also, the results of the current study suggest that there is an insignificant clinical difference at least in the first two hours of the postoperative period. The largest average difference in pain at any time interval was 0.72 units.

The average VAPS values of the Bupivicaine only group were virtually stable from the 30 minute time interval until and including discharge (1.76, 1.80 and 1.80 units). This was the only group to demonstrate this pattern on postoperative pain. With a half-life of 2.7 hours, it is reasonable that the pain control effected by the Bupivicaine lasted at least until the time of discharge.

This group used the second lowest volume of narcotics, reported the lowest rate of nausea (3 patients), used the second lowest volume of anti-nausea medications and had the longest average PAR times (172 minutes).

4.4.4 Ketorolac and Bupivicaine

In the overall comparison as well as at every time interval, the Ketorolac and Bupivicaine group had significantly less pain than the saline only group. The medication combination represents a considerable improvement over the current standard of care. This group used the lowest volume of narcotics (19 mg morphine, 25 μg fentanyl, 60 mg codeine), reported the second lowest rate of nausea, used the least anti-nausea medications (5 patients) and had the shortest average PAR time (148 minutes).

When compared with the Ketorolac only group, the Ketorolac and Bupivicaine group showed no difference in first 30 minutes postop. However, by the 60 minute time interval there was a significant difference. This difference persisted at discharge and was evident when the overall pain averages were compared. While there was evidence that the Ketorolac and Bupivicaine group had less pain on average than the Bupivicaine only group, the evidence was not great enough to show a statistical significance. At the time of discharge, the average pain in the Ketorolac and Bupivicaine group was decreasing while in the Bupivicaine only group it was stable. It is also worthy to note that while the percent difference in average PAR times between the Bupivicaine only and Ketorolac and Bupivicaine groups is small (25/148) 17%, it may be clinically relevant. A study performed to look specifically at PAR time as a primary outcome could carry out
statistical analysis on that data. A difference in PAR times of a half hour may not result in a statistically significant result, but it would certainly be clinically relevant. In an outpatient setting, the cost savings from a half-hour less of PAR time would be notable.

Another stimulating follow up study would be to follow the VAPS values of the patients in the Bupivicaine only and Ketorolac and Bupivicaine groups for a longer period of time. This would provide insight into the question of whether the intervention is merely blocking the peripheral pain sensation or whether it is interrupting the central sensitization. Another question is that of the pain in the first week postop. Was the benefit in pain control in the first two hours reflected in pain control in the late postop period? The exercise of gathering that information in this patient population would be difficult as they leave the facility so promptly and are often back to work in a couple of days. However, one could examine this same principle in a different patient population. For example, patients undergoing mastectomy routinely stay for at least 24 hours postoperatively and are off work for weeks to a month.

Although not designed to specifically look at the question of whether or not Ketorolac and Bupivicaine are stable and active compounds once mixed, the current study does provide some insight into this question. The Ketorolac only and the Ketorolac and Bupivicaine groups were significantly different. While the Bupivicaine only and the Ketorolac and Bupivicaine groups were not significantly different, there was a trend. The difference between these two groups may have been too small to be detected by this study. It would be stimulating to do a study designed to resolve this issue. Results from that study could also provide insight into whether the effects of the Bupivicaine and Ketorolac are additive or synergistic. As already discussed, if the patients had been followed for a longer period of time, a difference may have been seen.

4.5 GENERALIZABILITY

The study population was a consecutive sample of one hundred women undergoing primary augmentation mammoplasty. It represented a subset of the entire population that would receive this procedure.

An anaesthetic protocol was adhered to by the twelve anaesthesiologists. Would differences in anaesthetic medications or anaesthesiologist change the outcome of the current study? Certainly, average pain was flat as function of anaesthesiologist across the twelve physicians in this study. It would not be unreasonable to extend this trend to other anaesthesiologists. In terms of anaesthetic medications, the response is not as clear. With the current approach to anaesthesia and treating entrenched pain, the benefit of intraoperative Ketorolac and Bupivicaine could be expected to be generalizable to different anaesthetic medications. However, considering the volume of research currently focused on pre-emptive analgesia, it is very likely that anaesthetic protocols may undergo some drastic changes in the near future. What impact that would have on the current study remains to be seen.
Three experienced surgeons performed the operations. Theoretically, this study was only valid for patients of these surgeons. In view of the standard approach to dissection of the implant pocket, it would not be unreasonable to generalize the results of the current study to other surgeons equally experienced in this procedure. This may not be the case in less experienced surgeons and may need to be investigated. The incision was placed on the breast. The other incision occasionally used for this operation is the axillary incision. Regardless of the incision, the implant pocket is dissected out in a similar manner and is dissected to the same extent. That is, the size of the pocket is tailored to the implant to be placed and is not dependent upon the incision. One would expect similar result with pain control for the two incisions. The implant itself can be placed in either a submuscular or a subglandular plane. For this study, the implants were placed in the submuscular plane. When placing an implant in the subglandular plane, the pocket is dissected superficial to the muscle as opposed to deep to it and there is no muscle release with the subglandular implant. The difference in pain for these two options has not yet been studied. If the Ketorolac and Bupivacaine solution was used in conjunction with a subglandular implant, the solution would be being irrigated into a different tissue plane. What effect that would have on the solutions ability to decrease postoperative pain is uncertain.

The Ketorolac and Bupivacaine solution was irrigated into a pocket with a raw surface. It would be interesting to extend the use of this solution to other operative fields with similar raw surfaces. For example, in reconstructive plastic surgery, muscle flaps are often raised and transferred to other areas of the body to close large or difficult defects. This leaves behind a raw surface not unlike that created for an implant pocket. Would the Ketorolac and Bupivacaine solution be effective in reducing postoperative pain for these patients as well? This remains to be resolved.

The women in this study were undergoing primary augmentation. Any patient who had any prior breast surgery was excluded. In patients with prior surgery on the breast, there would be an element of scar tissue and perhaps previous pain issues. Those two aspects may have some impact on the effectiveness of the Ketorolac and Bupivacaine solution. With co-incidental procedures such as mastopexy, a procedure to affix sagging breasts in a more elevated and normal position with some improvement in shape, there would significantly more trauma to the breast. Again, postoperative pain studies have not been done in this population. Obviously, there would not be as discrete an area in which to distribute the solution and there is frequently tissue removed with this procedure. It would be difficult to generalize the results of this study to those procedures and further research would be needed. A procedure that would lend itself well to generalization of the current results is mastectomy, or excision of the breast. In a subcutaneous mastectomy, the nipple-aerolar complex and skin overlying the breast are preserved while the subcutaneous breast tissue is removed. This creates a large pocket that is routinely irrigated with normal saline and closed. While there is tissue removed, the pocket would be similar to that of an implant in a subglandular position and there may be a role for the use of the Ketorolac and Bupivacaine solution.

Augmentation mammoplasty is most often a cosmetic procedure. Patients decide to undergo this procedure on an elective basis. As such, the demographics are somewhat
different from patients undergoing reconstructive procedures. This does raise some question about the generalizability of the results in cosmetic patients to reconstructive patients. Perhaps the motivations and psychology are considerably different between the two patient populations. That may have some impact on their pain thresholds and in turn on the effectiveness of the Ketorolac and Bupivicaine solution.

4.6 COST AND BENEFIT CONSIDERATIONS

The benefit to the patient was apparent. The Ketorolac and Bupivicaine solution was a significant improvement over the more commonly used regime. The solution significantly reduced the pain experienced by the patient in the first two hours of the postoperative period. Reduced pain in the postoperative period may also have benefits that extend into the first week postoperatively and longer. Further research is needed to determine if there is an additional benefit of getting people back to work earlier.

The cost of a single dose of one ml of 30 mg/ml Ketorolac was $11.80. One-half percent Bupivicaine with epinephrine was supplied at a cost of $6.80 per dose. This constituted a total cost of $18.60 for a dose of the Ketorolac and Bupivicaine solution. Sloan et al. have shown that individual component costs do not represent adequately the total costs of care.\(^{(92)}\) Administrative efforts that micromanage therapeutic interventions and ignore the total process of care run the risk of increasing global health care costs. A cost of nineteen dollars seems unquestionably outweighed by the benefit of improved pain control for the patient.

With respect to cost savings by time in the recovery room, there was not an obvious difference between the saline only and Ketorolac and Bupivicaine groups. However, in light of the results, this was not the most important comparison. The difference in the Bupivicaine only and Ketorolac and Bupivicaine groups in terms of pain control was not significant although there was a trend to better pain control with the Ketorolac and Bupivicaine solution. There was a difference of almost a half an hour in the recovery room between these groups in favour of the later group. Further research would be required to confirm this difference as it was only a secondary outcome in this study, but a difference in PAR times of a half hour would certainly result in a significant savings in resources. In the outpatient setting this would be reflected in the closure of the PAR a half hour earlier, the relief of the nursing staff and shorter days for the anaesthesiologist as well as the surgeon. That benefit would be far offset the $11.80 for the Ketorolac.

A 1996 study by Burke et al. demonstrated similar results in that they found Ketorolac to be cost-effective in the management of postoperative pain due to its narcotic-sparring effect, decreased incidence of nausea and vomiting and reduced length of hospital stay.\(^{(93)}\) They also cited the attributable cost savings in inflation-adjusted dollars in a linear regression model as further confirmation of an overall benefit from Ketorolac use. Other studies have reported cost savings associated with Ketorolac. For example, intraoperative Ketorolac reduced the length of stay for outpatient\(^{(94)}\) as well as for inpatient laparoscopic surgery.\(^{(94)}\)
CHAPTER 5: CONCLUSION

In women undergoing primary augmentation mammoplasty, intraoperative use of Ketorolac combined with Bupivicaine with epinephrine irrigated into the surgical wound reduced pain in the postoperative period. The power of this study was 0.90 and 95% confidence intervals were used to determine significance. The traditional standard of saline irrigation and postoperative opioid analgesic use without pre-emptive analgesia is challenged.
REFERENCE LIST

2. Wall, P. D. The brief and the prolonged facilitatory effects of unmyelinated afferent input on the rat spinal cord are independently influenced by peripheral nerve section Neuroscience 17: 1199-1205, 1986.


A.3 Purpose of the Research

The purpose of this clinical trial is to obtain data regarding the effectiveness of Ketorolac and Bupivicaine at reducing pain after breast augmentation surgery. It is not known whether the use of these drugs is beneficial or not.

A.4 Conduct of the Study

Each patient that consents to the study will participate for 10 days. Approximately 100 patients will take part in the study at the Okanagan Plastic Surgery Centre (OPSC). Before a patient may be included in the study, she must have met several criteria (for example, first augmentation, no other breast surgery, and no other procedures at the same time).

Patients who meet these criteria and consent to the study will be randomly assigned to one of four possible groups:

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Standard treatment</td>
</tr>
<tr>
<td>II</td>
<td>Standard treatment + Bupivicaine</td>
</tr>
<tr>
<td>III</td>
<td>Standard treatment + Ketorolac</td>
</tr>
<tr>
<td>IV</td>
<td>Standard treatment + Bupivicaine + Ketorolac</td>
</tr>
</tbody>
</table>

The random assignment means that the patient will have a one in four chance of receiving only the standard treatment (normal saline which is salt water), a one in four chance of receiving the standard treatment plus Bupivicaine, a one in four chance of receiving the standard treatment plus Ketorolac and a one in four chance of receiving the standard treatment plus Bupivicaine and Ketorolac. Thus, the patient will always receive at least the standard treatment.

This study is structured as a “triple-blind” study, which means that the surgeon, the patient and the study nurse will not know to which group the patient has been assigned. However, this information is available to the surgeon in an emergency. This “triple-blind” procedure is necessary to assess the true effects of the study drugs.

The study drugs will be provided by OPSC at no cost to the patient.

The study consists of two different periods (treatment period and follow-up period). During both periods, the patient will be closely monitored for any unwanted effects and will receive appropriate treatment if necessary. The structure of each period is as follows:
Treatment period: After meeting the criteria for the study, the patient will be taken to the operating room. Once the pocket for the implant has been created, the surgeon will use a syringe to irrigate (pour) the fluid into the implant pocket. All four solutions are made up to the same volume and have similar appearances. After the surgery is completed and the patient is awake, a nurse will administer the Visual Analog Pain Scale (VAPS). This will be repeated at one half hour, one hour and at the time of discharge (when you are about to leave).

Follow-up period: Once home, the patient will complete the VAPS on a daily basis in a “diary” provided by OPSC. On the first and third day after surgery, a nurse will phone the patient to make sure there are no problems from the surgery or with the diary. On the tenth day, the patient will have a scheduled appointment with her surgeon at which time she will return the completed form. This is a standard follow-up appointment. If the patient cannot return for the appointment, a nurse may be sent to the patient to check on the healing of the incision and to collect the diary.

A.5 Unwanted Effects due to Bupivicaine and Ketorolac and Possible Risks

Because Ketorolac has only been administered to a small number of humans in this manner, limited information on specific risks are available and it is possible that there are risks that are not yet known. According to our present knowledge, specific adverse effects of the study medication or interactions with other medications are not expected.

There is no evidence of effect on the unborn child for the study medications.

If and when additional information becomes available about possible risks associated with the study medications, this information will be provided immediately to the doctor and he will provide this information to you in a timely manner.

A.6 Possible Benefits

By taking part in this trial, the patient will be supporting the development of a drug protocol that could help both her and others in the future. In this study we hope to find out whether postoperative pain is decreased in patients that receive the study medications in the operating room. It is possible that the patient may benefit in these ways, but it is also possible that she may not.

A.7 Alternatives

Besides the current study, there are no other medications proven to be effective in addition to the standard treatment that the patient could receive as an alternative.
APPENDIX B
OPSC: POSTOPERATIVE PAIN STUDY
DATA COLLECTION FORM

PATIENT DATA
Syringe #: ____________________
Birth Date (d/m/y): ____________
Height: ____________________ Weight: ____________________
Married / Single
Nulliparous / Pregnancies: __ Children: ___ Nursed: Y / N

MEDICAL INFORMATION
Generally Healthy: Y / N
Medications:
Oral Contraceptives / Hormone Medications: Y / N
Allergies:

OPERATIVE DATA
Date (d/m/y): ________________ Informed Consent for Study: Y / N
Anaesthesiologist: __________
Implant Type: ________________
Implant size (Left / Right): ______ / ______
Anaesthesia Time: ________ OR Time: __________
Dissection Code (from surgeon): 1 / 2 / 3

PAR DATA
PAR RN: ____________________ PAR Time: ______
Anaesthesia Pain Scale
Post-op: ___ 30min: ___ 1hr: ___ discharge: ______
Medications given (type/time/dose):
Nausea: Pre / Op / Post

*** If patient is excluded, please indicate reason on reverse. ***