PERIAPICAL MICROSURGERY: THE EFFECTS OF LOCALLY INJECTED DEXAMETHASONE ON POST-OPERATIVE HEALING

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A thesis submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Masters of Science in the School of Dentistry (Endodontics).

Chapel Hill
2015

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ABSTRACT

Elena V. Kan: Periapical Microsurgery: The Effects of
Locally Injected Dexamethasone on post-operative Healing
(Under the direction of Peter Z. Tawil)

Substantial inflammation, bruising and pain have been an inevitable consequence of oral surgery. **Objectives:** To study a protocol to reduce these complications after periapical microsurgery. Hypothesis is that a single local submucosal injection of 4.0mg of dexamethasone at the time of periapical microsurgery can reduce the postoperative complications. **Materials and Methods:** Sixty patients received injections of either dexamethasone or a placebo solution at the conclusion of a standardized periapical microsurgery within a double-blind randomized controlled clinical trial. A self-administered survey provided data for analytical comparison. Data was analyzed at a significance level of 95% using Chi square and the Fisher Exact tests. **Results:** Subjects who received the dexamethasone injection reported less swelling 24 hours post-periapical microsurgery compared to the placebo at a statistical significant level of greater than 98%. **Conclusion:** A dexamethasone injection minimizes post-operative swelling 24 hours following periapical microsurgery.

ACKNOWLEGEMENTS

I wish to thank and acknowledge my fellow endodontic residents: Dr. Melita Islambasic, Dr. Bryan Mitchell, Dr. Tangit Taggar, Dr. Jeffrey Parker, and Dr. Alison St. Paul for their clinical performance in surgeries. I wish to recognize my committee and advisors Dr. Peter Z. Tawil, Dr. Jonathan M. Reside, Dr. Asma A. Kan for their expertise and patience. I wish to make special recognition to Dr. Derek Duggan whose guidance was invaluable.

I wish to thank and acknowledge the American Endodontic Association for their financial support and the Angelus Company for their product support. Also, I wish to thank Dr. Veeral Saraiya for providing statistical analysis.

Finally, I wish to recognize the University of North Carolina at Chapel Hill, the UNC Dental School and the Endodontic Department for the use of clinical facilities.

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LIST OF ABBREVIATIONS AND SYMBOLS

AAE	American Association of Endodontics
ACTH	Adrenocorticotropic hormone
CRP	C-reactive protein
ESR	Erythrocyte Sedimentation Rate
HIPAA	Health Insurance Portability and Accountability Act
IDS	Investigational Drug Services
IRB	Internal Review Board
MAP	Micro apical placement
MG	Milligrams
MTA	Mineral trioxide aggregate
NSAID	Nonsteroidal anti-inflammatory drug
UNC	The University of North Carolina at Chapel Hill

CHAPTER 1: INTRODUCTION, STUDY DEVELOPMENT AND ANALYSIS

Introduction

Post-treatment complications in endodontics continue to be a significant problem in dentistry. Initial endodontic therapy does not produce an acceptable treatment outcome in approximately one-third of all cases and, therefore, endodontic retreatment is required (1). Analysis of surgical and non-surgical retreatment therapies (2) have found that healing rates are not substantially different between the two approaches (3).

Traditionally, the cost of retreatment is higher since treatment typically takes multiple appointments. This is in contrast to a surgical retreatment which can be performed in a single appointment. Furthermore, a traditional retreatment approach requires access through the crown and can involve replacing the crown. This is in contrast to periapical surgery that only involves resection of soft tissue, bone and root structure without penetrating the crown structure. In addition, there is a high frequency of flare-ups experienced by patients who are treated with the traditional orthograde retreatment of root canal therapy (4). Periapical surgery is a more efficient and less expensive method for retreatment relative to the orthograde method which involves removing posts, root canal filling material, and often replacing a crown (3, 5).

Periapical surgery is regarded as an integral part of modern endodontics (6, 7). Endodontic surgeries account for approximately 6 to 10% of the typical endodontic practice treatments (8, 9) and are considered an extension of non-surgical treatments. Based on short

and long term evaluations, periapical surgeries have a 91 to 97% healing success rate (10, 11) making periapical microsurgery a good treatment option.

Research indicates that inflammation, pain, swelling, and bruising have long been an inevitable consequence of oral surgery (5). The same research indicates that post-endodontic surgical discomfort can cause 23% of patients to miss work (5). Some studies have found that patients with pre-operative endodontic pain will continue to have post-treatment pain in up to 80% of the cases (12-14). The greatest concern among endodontic surgery patients is experiencing pain (10). According to one study, patients experience their peak pain by the end of the day of their endodontic surgery (5). Although all patients endure some level of pain, approximately two-thirds of the patients that undergo endodontic surgery require analgesics to lessen their pain (15).

Pain is a complex process that involves sensory, emotional, and conceptual aspects (16). Post-treatment analgesic intervention is necessary in many endodontic cases to manage pain. There are various classes of drugs that have been proposed in the management of post-treatment endodontic pain and discomfort. These classes include NSAIDs, Acetaminophen, opioids, and corticosteroids (12, 14, 15, 17). Research has proposed that corticosteroids are effective in treating pain (12, 14).

The majority of evidence evaluating post-surgical discomfort and complications utilizes the oral surgery third molar extraction model and views the aspect of pain as a consequence of the acute inflammatory reaction. However, pain in endodontic origin differs from this model in that it is associated with chronic inflammation (18), the presence of bacterial by-products, and the activation of inflammatory mediators and immune cells (19).

Wound healing or repair after surgical procedures is an important component of inflammation (20) and is a necessary physiological response of the body to the injury (21).

Review of Inflammation

Inflammation has been defined as "the local reaction of vascularized tissue to injury" (22). Manipulation of the soft and hard tissues during endodontic surgery leads to an inflammatory cascade via biological mediators (e.g. prostaglandins, leukotrienes, bradykinins, histamine, serotonin, and others) that are released from blood vessels and cells in the injured area (22) and serve a specific role at each stage of the inflammatory process (20). This inflammatory cascade results in pain and vasodilation which leads later to edema and hematoma in the injured area (21).

Inflammation can be divided into three stages: acute, chronic, and repair with no clear dividing line among them (20, 23). Periapical microsurgery involves all three stages: chronic inflammation due to the periapical lesion that is present at the time of treatment, acute inflammation at the time of hard and soft tissue manipulation, and repair after conclusion of the surgical intervention.

Acute inflammation is characterized by the transudation of leukocytes into the tissue, whereas chronic inflammation features the presence of leukocytes in the tissues (23). Acute inflammation is an exudative process where small vessels become permeable. This allows plasma proteins and fluid to leave the bloodstream and enter the tissue to form a loose network of fluid, fibrin, and white blood cells (20). Chronic inflammation, on the other hand, is a proliferative process with the presence of fibroblasts and angioblasts (20) and nerve sprouting (24). Acute inflammation involves an influx of neutrophils, while chronic

inflammation involves mononuclear inflammatory cells, such as macrophages, lymphocytes, and plasma cells (23, 24).

The first event in any inflammatory reaction is tissue injury. After the initial injury, a transient vasoconstriction occurs and is followed by vasodilation of the tissue. The injured tissue becomes painful, hot, erythematous, and edematous (20, 21). There are many biochemical mediators that take place to contribute to the symptoms and signs of inflammation.

Arachidonic acid is a major precursor of inflammatory reaction and its metabolites are important mediators in the inflammatory cascade (Figure 1). Major arachidonic acid derivatives include prostaglandins and leukotrienes. Both prostaglandins and leukotrienes are responsible for delaying and prolonging stages in vascular permeability. They are long-chain, lipid-soluble fatty acids that are present in all tissues and are formed within seconds after various stimuli. In inflammation, macrophages and neutrophiles are responsible for the production of both prostaglandins and leukotrienes. Arachidonic acid serves as the precursor to both prostaglandins and leukotrienes and is produced by the action of phospholipase A2. Phospholipase A2 is an enzyme that is found in all human cells.

The oxidation of phospholipase A2 leads to the formation of arachidonic acid from cell membrane phospholipids. Once arachidonic acid is formed, it is metabolized by two major enzymes: cyclooxygenase or lipoxygenase. The cyclooxygenase pathway involves prostaglandins, which produce vasodilation of tissues and increase of vascular permeability. The lipoxygenase pathway involves leukotrienes (21).

All of the components of inflammatory cascade cause patient discomfort. Inflammation is a major cause of pain, swelling and bruising that accompany any surgery.

One method to decrease these critical signs of inflammation is through the use of anti-inflammatory agents. These agents aid in the reduction of unpleasant side-effects of the inflammatory cascade through the inhibition of the steps in the formation of arachidonic acid and its metabolites. The potential for anti-inflammatory agents to prevent pain, swelling, and bruising depends on the suppression of the release of the inflammatory mediators. A decrease in the amount of inflammatory mediators present leads to a reduction in vascular permeability. This in turn decreases fluid accumulation within tissues, resulting in a decreased tissue pressure that translates to less pain, swelling and potential bruising (14). Various medications have been used to interfere with inflammation to prevent or stop pain, swelling and/or bruising. Two commonly used classes of medications for this are NSAIDs and corticosteroids.

NSAIDs are cyclooxygenase inhibitors and prevent formation of prostaglandins and thromboxanes from arachidonic acid (25), but do not affect the lipoxygenase pathways (Figure 2). In contrast, corticosteroids prevent the release of arachidonic acid which inhibits both inflammatory pathways and effectively prevent inflammation (26-28). As a result, the anti-inflammatory efficacy of corticosteroids is more pronounced than NSAIDs, which has led to their use after surgical procedures (29-32).

Many different steroids are currently available on the market. One of the first clinical applications of corticosteroids was the use of compound E, cortisone, compound F, and hydrocortisone, in the treatment of rheumatic fever was in the late 1940's (33). Past studies have primarily focused on the use of glucocorticosteroids (cortisone and hydrocortisone) in dental applications. Dexamethasone is one of the most recent corticosteroids to become available on the market. Dexamethasone has been successful in reducing the post-operative

sequelae (10, 29-32, 34-40) that typically accompanies oral surgery. The anti-inflammatory effect is a result of the suppression of the migration of neutrophils, leukocytes, and macrophages through the inhibition of the formation of arachidonic acid, thus blocking the cyclo-oxygenase and lipoxygenase pathways and respective synthesis of prostaglandins and leukotrienes (41, 42). Corticosteroids can be delivered through a variety of methods, including orally, intravenously (37, 43), intramuscularly (12, 14, 31), submucosally (36), intraligamentary (29, 30, 38, 40, 41, 44), supraperiostealy (45) and intraosseously (46, 47). The submucosal injection enables the application of anti-inflammatory agents at a precise site to effect a pharmacological action in sufficient quantities. More importantly, dentists are familiar with submucosal injections over other techniques.

Review of Steroids

The adrenal cortex synthesizes corticosteroids from cholesterol. Corticosteroids contain 21 carbon atoms in a 4 member hydrocarbon ring. Adrenal corticosteroids are necessary regulators of homeostasis (48). These corticosteroids are produced naturally and include different classes, mineralocorticoid (aldosterone), the sex hormones (testosterone, estrogen, progesterone), and glucocorticosteroids (cortisol). Aldosterone affects the human body's water and electrolyte balance. It is primarily secreted by stimulation of the kidney's renin-angiotensin system. Therefore, water and electrolyte balance are not affected by suppression of adrenal glands (48). Sex hormones are produced by gonads and adrenal glands (48).

Glucocorticosteroids act on multiple sites to inhibit immune and inflammatory reactions. Cortisol is the primary glucocorticosteroid that is synthesized by the body and is secreted by the adrenal cortex. This process is controlled by the hypothalamus and anterior

pituitary glands. Along with the adrenal cortex, these structures make up the hypothalamic-pituatatry-adrenal axis. This system regulates glucorticosteroid synthesis. The hypothalamus produces corticotropin-releasing hormone, which travels to the anterior pituitary gland via the hyphothalamic-hypohyseal portal system. This corticotropin-releasing hormone stimulates release of the adrenocorticotropic hormone (ACTH) by the pituitary gland (49). ACTH is the main regulator of cortisol. The metabolism of corticosteroids occurs in the liver, and later, through excretion in the urine (41, 42, 48).

The chemical modification of cortisol produces a number of synthetic corticosteroids. Synthetic corticosteroids, as well as cortisol, are 90% bound to plasma proteins (albumin and corticosteroid-binding globulin). Only a small unbound portion of corticosteroids are free to enter the cell and mediate the anti-inflammatory effect at any time. Although cortisol normally has a half-life of 90 minutes, chemical modifications to its composition can cause it to have a greater anti-inflammatory effect and an increased duration of action.

Indications and Contraindications of Steroids

There are many applications of corticosteroids in dentistry. Oral surgery studies have used dexamethasone for reducing edema, pain, and trismus after extraction of third molars utilizing various injection methods (31, 36, 37) and oral formulations (32, 35, 38). Research has demonstrated a pain reduction of 50% when dexamethasone was used pre- and post-operatively after extraction of 3rd molars (32). More than 1/3 of patients traditionally require post-operative analgesics after surgical extraction of third molars. Evidence suggests that 8.0 mg of dexamethasone administered orally significantly reduced post-operative pain (35).

Early case reports indicated the use of corticosteroids in dentistry for alleviating symptoms related to refractory facial and oral lesions with unknown etiology (51).

Pre-operative administration of oral dexamethasone in a periodontal surgery model finds that it is effective in reducing pain after periodontal surgeries for the initial eight hours following treatment (30). The same author found in another study that it is better to use a single oral dose of 8.0 mg of dexamethasone than two doses of 4.0 mg of dexamethasone in reducing pain one-hour prior to periodontal surgery (29). Patient compliance and the need for repeated doses to sustain adequate steroid concentration can become problematic with oral administration. It is more predictable and effective to inject the dexamethasone at the time of the surgery rather than using the oral route.

An animal study showed that the supraperiosteal infiltration of dexamethasone into the submucosal tissue had a significant anti-inflammatory effect on the injured periapical tissues (61). The study also stressed the importance of patient compliance and use of an infiltration method instead of oral administration. Submucosal deposition of dexamethasone is the preferred method of delivery, as an application at the site of inflammation provides the maximum anti-inflammatory effect on tissues. Intramuscular administration has been shown to have the same effect as oral infiltration (14). However, a practitioner should be experienced in giving an intramuscular injection as accuracy is paramount. The oral infiltration injection is a familiar procedure in dentistry. Another animal study found similar effects of dexamethasone that was deposited and absorbed in the maxilla and mandible (62). This finding can be used to prevent flare-ups after endodontic treatment and periapical microsurgery using similar doses for the maxilla and/or mandible.

Studies have demonstrated that corticosteroids can prolong pulpal anesthesia with inferior alveolar nerve blocks in patients that experience the painful condition of irreversible pulpitis (53). However, one study showed that an intrasulcular injection of ketorolac is very

painful and not recommended as a supplemental treatment in patients with irreversible pulpitis (54).

Corticosteroids have been an effective treatment for the injured and/or compressed inferior alveolar nerve after the extrusion of root canal filling materials (55).

There are documented cases of corticosteroids being used in instances of sodium hypochlorite incidents with or without neurological deficit during endodontic procedures (56, 57), thus, promoting recovery.

In some instances, placing corticosteroids locally into the root canal space prevents and possibly treats flare-ups after endodontic treatments (17, 52, 58-60).

Supra-periosteal infiltration with a single dose of 4.0 mg of dexamethasone has been found to be effective in reducing acute pain after endodontic treatment if administered within the first 24 hours, but not more than 48 hours (45). Most endodontic patients with acute pain experience pain even after endodontic treatment had been performed (5, 58).

Some endodontic microsurgery protocols incorporate oral dexamethasone to be administered preoperatively and postoperatively (34, 39, 40). One endodontic surgical model suggested that the routine use of oral dexamethasone is a safe method to reduce pain and swelling after endodontic surgery (10).

Corticosteroids at higher levels with multiple dosages have been found to cause adrenal fatigue and can mask symptoms of bacterial infection (48, 49). One study showed that a one-week course of corticosteroids is not harmful, but instead, very effective in reducing post-surgical dental pain and swelling (15). The important aspect of this study was that patients required less NSAIDs and opioids to control pain. A single dose of corticosteroids has been proven to be safe and effective in terms of reducing pain and swelling

(39). One of the earlier studies concluded that a single large intravenous dose of dexamethasone (2.0 milligrams per kilogram of body weight) does not have any harmful side effects (43).

Some studies raised concerns regarding expanded uses of corticosteroids in dentistry due to their adverse reactions. These studies concluded that corticosteroids can cause psychosis, memory disturbances, and hallucinations (63-65). These case documented reports are based upon small doses that patients were taking for prolonged periods of time. Patients who suffer from mental illnesses, pregnant woman, immune-compromised patients (i.e. Cushing's syndrome, tuberculosis, systemic fungal infection, uncontrolled diabetes), chronic pain patients, or patients with hyperthyroidism should not take systemic corticosteroids for a prolonged period of time (48, 66-69). Based on the above, this study's small single dose of corticosteroids at the conclusion of the periapical microsurgery is safe, effective and efficient in reducing post-operative complications.

Study Development

Sample Size

Determining the sample size for a research survey is the task of choosing the number of observations or patients to include in the statistical sample. The goal of this study was to make statistical inferences about the population from the sample. As with any empirical study, the sample size was of paramount importance. In some experimental designs, where a study may be divided into different treatment groups, there may be different sample sizes for each group. In this case, for the sake of statistical tests and administrative ease, the same number of patients were placed in each group.

The statistical power of a sample size relies on many subjective estimates. There has been little endodontic research in this specific area. Therefore, there was no specific proxy as to expected variance or sample size. The only guidance was based upon anecdotal evidence from oral surgeons' experience with an injection-form of dexamethasone.

After balancing the statistical methods to be employed, costs, and timeline, it was estimated that the sample size of sixty patients (n = 60) would provide the necessary statistical significance to make valid conclusions. Patients were selected from those that were currently or previously recommended for endodontic periapical microsurgery by the UNC Dental School Endodontic Department. Participants were randomly placed into two groups by UNC Investigational Drug Services (IDS). The first group of participants, which totaled thirty (x = 30), received an injection of 4.0 mg of dexamethasone solution. The second group of participants, which also totaled thirty (y = 30), received an injection of placebo saline solution. The formula for the sample population is as follows:

$$n = x + y$$

Where,

x = Number of dexamethasone group patients

y = Number of placebo group patients

n = Total population of the sample

Patient Selection

This study involved sixty (n = 60) patients that were prequalified and selected for endodontic periapical microsurgery from the UNC Dental School Endodontic Department's patient files. This study included the first sixty qualified patients on a first-come-first-served basis that agreed to participate. Current patients that would likely qualify were considered immediately. Endodontic residents in the department were aware of the research and alerted the patient and the principal investigator of a potential case. Clinical and radiographic exams were used to determine patient qualifications. The selection process sought males or females of at least eighteen years of age. Patients were required to be in relatively good health with no significant medical conditions.

All root canal treated cases with apical periodontitis were eligible for inclusion where previously endodontically treated teeth had non-healing lesions, endodontic retreatment was impossible (post, anatomy), or cases with a high possibility of failure after a traditional root canal treatment. All teeth groups (anterior, premolars, molars, maxillary or mandibular teeth) were eligible for the study.

Patients that were pregnant, immune-compromised or suffering from chronic pain were removed from consideration. Patients taking systemic corticosteroids were excluded from the list of candidates. If the patients displayed acute symptoms, acute apical abscess, Miller class II

or III mobility, horizontal/vertical root fractures, combined endodontic-periodontal lesions, compromised crown-to-root ratio or patients with systemic conditions were removed from consideration.

Written and verbal informed consents were obtained from qualified participants. Among much other information, patients were informed that they may or may not actually receive the drug dexamethasone. Patients were informed that they might actually receive a placebo. Given the nature and importance of these communications and the survey, those not literate in English were removed from consideration.

Criteria and Restrictions

Patients were subject to certain study criteria and restrictions with the aim of upholding the validity of the study while maintaining a safe procedure for patients. As with most clinical studies, one goal of the criteria and restrictions is to create a uniform environment. The study boundaries can be used to isolate the event to be studied from the influence of other factors. This provides the truest cause-and-effect result.

Clinical and radiographic examinations as well as a medical history review were used to determine whether a potential candidate's qualifications adhered to the criteria and restrictions.

Another goal of the study conditions is to maintain patient health and safety. The study submitted to the stringent conditions and restrictions place upon it by the IDS and IRB. Patient candidates whose physical qualities might overshadow the study results were removed from consideration. Disqualification was also done in some instances out of consideration of the candidate's health and safety.

The selection process sought males or females of at least eighteen years of age. This created a pool of individuals above the age of consent. This avoided exposing minors to any

unforeseen risks of the study.

Candidates were questioned pre-operatively about their health and medications that they were taking. As all candidates were current patients at the UNC Dental School, merely updating their records was the primary task. As current patients, this provided a preliminary screening of that patient's vital readings (blood pressure and pulse) to ensure they were within safety standards as set in the IDS and IRB as well as the school's standards. Candidates that were pregnant were removed from consideration. Although the drug dosage was small and local, pregnant candidates were removed from the selection out of an abundance of caution for the fetus. Females of child-bearing age were offered a pregnancy test to determine if they were pregnant. Every female patient was required to give verbal confirmation that she was not pregnant or planning to become pregnant prior to inclusion in the study.

Surgical Procedure

All research and surgical consents were filled out by the participants prior to the surgical procedures. With the exception of the incisions and suturing, all microsurgical procedures were performed using a Surgical Operating Microscope (Global G6 Microscope, Global Surgical Corporation, St. Louis, MO). All surgeries were performed using modern microsurgical techniques (70, 71). All participants were required to rinse their mouth with 0.12 % chlorhexidinegluconate rinse (Peridex 3M ESPE) for one minute immediately prior to the periapical microsurgery. Chlorhexidine mouth rinse plays an important role in pre-disinfection of the surgical area. About 30% of chlorhexidine may be retained in the mouth after rinsing for one minute (72) and once bound to the oral tissues, chlorhexidine can be released for up to 12 hours for a prolonged bacteriocidal effect (72, 73).

Local anesthesia with 2% lidocaine and 1:100,000 of epinephrine was administered in

the area of the surgery via local infiltration. In addition, a 2% lidocaine solution with 1:50,000 of epinephrine was administered in the planned incision area in order to achieve improved hemostasis. Local anesthesia serves two purposes: to prevent pain during surgery and to minimize surgical hemorrhage due to vasoconstriction. A 2% lidocaine solution with epinephrine is the anesthetic of choice since it activates alpha receptors that are present in the muscles of the arterioles, periodontium, and submucosa causing vasoconstriction (74, 75).

After anesthesia, a #15C surgical blade was used to make papilla-base incisions and vertical releasing incisions to allow adequate access to the surgical area (76, 77). A coronal split-thickness and apical full-thickness mucoperiosteal flap was used to ensure standardization and to allow for the most esthetic outcome (78-80). Participants were made aware of the risk that gingival recession might occur after the periapical microsurgery (81, 82).

If necessary, osteotomies were performed using a #6 round carbide bur in a high-speed impact air hand piece (Sybron Endo, USA) under copious water irrigation. The modified surgical hand piece used a 45-degree angulated head for visibility and no air ejection to prevent emphysema. Carbide burs were used during the osteotomy to ensure safe and clean cutting. Water irrigation was necessary to minimize thermal injury to the adjacent bone (83, 84).

A curettage of the granulation/pathological tissue was completed and the tissue was submitted in 10% neutral buffered formation to the UNC Department of Pathology for histological evaluation. Periradicular curettage is necessary for the removal of pathological tissue, increased visibility during the surgery, maintenance of hemostasis, and to promote healing of the periradicular tissues (85, 86).

The apicoectomy was performed with a 0-30% bevel (87) by sectioning 3.0 mm of the root tip (88) with a high-speed surgical hand piece using a multi-purpose bur (Dentsply Maillefer, Milford, DE) under copious water irrigation. A resection of at least 3.0 mm of the root tip was completed to ensure the best healing potential due to the potential for accessory anatomy in the apical portion of the root (88). A minimal bevel was desired because it required a smaller osteotomy, minimal loss to a buccal cortical plate, and eliminates missed anatomy (87, 89).

The resected surface of the root was stained with methylene blue dye (Vista BLUE, VISTA Dental Products, USA) and inspected under a microscope using a micro-mirror to detect any cracks, fractures, dentinal defects or missed anatomy. The microscope's trans-illumination and the methylene blue aided in detecting the etiology of the non-healing endodontic lesions (90).

The root-end preparation was performed at least 3.0 mm into the canal space following the long axis of the tooth using ultrasonic surgical tips (Obtura, Spartan) under sterile saline irrigation. Using ultrasonic surgical tips for the end-root preparation ensured a smooth surface (91) and appropriate depth/diameter for placement of the retro-filling material. Cleaning deep isthmuses (92) with any other means does not guarantee a favorable result (93, 94).

Mineral trioxide aggregate (MTA) was used as a root-end filling material and placed into the root-end preparation using the micro-apical-placement system (MAP by Roydent Dental Products, Switzerland). The MTA was mixed according to the manufacturer's directions at a 3:1 powder to liquid ratio using a sterile water solution. Such a mix provided the best handling and biological properties (95). The placement of the retro-filling material

created a seal to prevent the ingress of microorganisms or their byproducts into the canal. There are many acceptable retro-filling materials on the market (96, 97). Evidence suggests that MTA provides the best seal (98). In addition, MTA is biocompatible and has a high pH balance upon setting (99-101). This study used a white MTA-Angulus (Angelus Dental Solutions, Londrina, Parana, Brazil) due to its excellent handling property and predictable setting time (98, 100, 101). A post-operative radiograph was taken to confirm the adaptation of the root-end filling to root-end preparation. Following completion of apicoectomy, the mucoperiosteal flap was irrigated with copious sterile saline solution.

The soft-tissues were then repositioned with 5.0 and 4.0 chromic gut sutures to obtain primary closure. The sutures maintain the position of the flap during the initial healing via primary intention. The approximation of the papilla with a smaller suture size gave the best esthetic outcome (80, 102). A local administered submucosally injection of dexamethasone 4.0 mg or placebo saline solution was then placed at the conclusion of the surgery.

All participants, regardless of the group in which they were assigned, received the same standard post-operative care instructions in verbal and written form. All participants were also given a standardized post-operative surgery prescription for pain control for the following three days to be taken if needed. The prescription included twelve 500 mg tablets of Tylenol and twelve tablets of Vicodin 3/500. Participants were instructed to take both tablets every 6 hours if they experienced pain. Participants were informed not to take more than 4 dosages of either medication in a 24 hour period.

Calibration

In order to ensure standardization, experienced endodontic residents (second and third year residents in the UNC School of Dentistry Graduate Endodontics program) performed all

of the periapical microsurgeries. Prior to participation in this study, each resident had performed at least forty endodontic surgeries. Besides having been trained in the same endodontic program, all participating endodontic residents attended a 6-hour lecture and watched a video on the standardized surgical protocol prior to the study. In addition to this calibration and standardization, the principal investigator performed or assisted in all of the research surgeries. In order to avoid variances/errors during each procedure, the principal investigator, when not performing research surgery, was assisting in order to verify accurate papilla-base flap design and flap reflection, standard osteotomy, curettage, root-end resection, root end-preparation and the placement of MTA (confirmed with a radiograph), and suturing. At the conclusion of every surgery, the primary investigator administered the study protocol injections at the mucobuccal fold, adjacent to the target tooth with advancement of the needle to approximate the osteotomy site. As a last safety measure, an attending endodontic faculty closely monitored all surgical procedures to ensure quality of care.

All of the residents and the patients that were participating in the study were informed that the principal investigator could intervene at any time during the surgery in order to be consistent with the study protocol. Only the principal investigator performed the follow-up evaluations for uniformity of the results. Given the above, the standardization and oversight within an endodontic resident program minimized the chance of error or variance in the procedure.

Required Information and Measurement

As with all experiments, uniformity and consistency in gathering of information and measurements was vital in this study. Careful consideration and implementation of methods and procedures was applied to achieve this goal.

Pain, swelling, bruising and intra-oral healing were the four general areas of recovery that the study assessed (Figure 3). It was necessary that the study measure these areas from the standpoint of the patient experience as well as the perspective of the investigator for consistency and confirmation. Photographic and survey documentation at pre and post-operative examinations provided data for analytical comparison.

Survey

The patients were instructed to complete the self-evaluation surveys on a 6-point likert-like visual analog scale for each of the post-operative categories of pain, swelling, bruising, and intra-oral healing (Figure 3). The visual analogue scale is a psychometric response scale used in subjective questionnaires. Instructions on completion of the survey were given to patients post-operatively. Patients were informed of the characteristic pain, swelling, bruising, and intra-oral healing that one would anticipate after such a procedure. When responding to an item in this survey, patients were to indicate their rating by indicating a position along a continuous line between two end-points. Patients made observations at four consecutive 24-hour intervals and recorded their experience on the survey. One week after the surgery, patients met with the investigator to submit the subject's survey responses and complete a clinical evaluation. This method allow for the study of absolute levels of healing as well as the rates of recovery.

Pain

The pain scale's purpose was to measure the patient's pain intensity and duration. Often, and as in this study, the pain scale was based on self-reported, observational, and physiological data. Self-report was considered primary and was obtained through the daily survey sheet. In addition, the investigator in this study completed patient interviews regarding

the different dimensions of pain they experienced to develop consistency among patients in the investigator's rating. The questions included the site of the pain, such as: "Where specifically is the pain?" The patient was questioned about the type of pain, such as: "What does the pain feel like?", or, "Did the pain impact your everyday life?" Patients were also asked questions regarding exacerbating or relieving factors, such as: "Was there anything that made the pain worse or better?", or, "Was it necessary to take pain relief medication?" Patients were instructed to take 500 mg of Tylenol and Vicodin 5/300 in order not to affect the observations inflammation. The relative pain level assessment at each interval was regarded as an important element in judging recovery. Because pain is a subjective and an internal experience, the evaluation of pain in this study was best performed by using patient self-reports. This appears to be the most frequently used technique in other pain studies (12, 15, 25, 29, 30, 38).

Swelling

Swelling of tissue creates a tight barrier which keeps bacteria out. The increased blood supply provides a defense mechanism. Inflammation's basic role of isolating injury, eliminating invaders and healing damaged tissue is vital.

Measuring the change in acute phase reactants is one method of detecting inflammation. The body reacts to inflammation by changing the manufacturing of protein in the liver and other protein creating organs. Acute phase reactants are proteins whose blood levels are altered by inflammation. Two techniques for measuring the change in acute phase reactants are the Erythrocyte Sedimentation Rate (ESR) and the C - reactive protein (CRP) (112, 113). These techniques measure the rate at which red blood cells settle over a small interval of time. The rate is directly proportionate to the amount of reactant proteins that are

present. The presence of inflammation increases the amount of proteins in the blood, accordingly, the rate of production increases. Unfortunately, the rates are not specific and can be altered by other circumstances such as anemia. The levels for both ESR and CRP can be influenced by both gender and age. Finally, and most importantly, inflammation due to other causes is not distinguishable from swelling caused by the surgical procedure. The size of the surgical wound and swelling would be relatively small and short in duration in contrast to other whole body causes.

Like pain, inflammation is almost always present with a surgical procedure. The swelling scale's purpose was to measure the degree and persistence of inflammation in and around the site. In this study, the swelling score was based on self-report by the patient's daily survey observations as well as the investigator's perspective. This was deemed to be a better approach in contrast to ESR testing given the specific and local nature of the wound, duration of recovery and expense and time of ESR testing.

Bruising

Periapical surgery results in some degree of injury to the blood vessels in the gingiva. A bruise is a traumatic injury of the soft tissues that results in breakage of the local capillaries and leakage of red blood cells (22). This results in a black and blue discoloration appearance that, as it fades, becomes green and brown. This is due to metabolization of the blood cells and bilirubin pigment in the skin (114). Bruising is regarded as an important factor in judging recovery as well as gauging the initial tissue damage by the periapical surgery procedure.

Innovative measures of bruising, such as Electrical Impedance Measurement, were not a practical application in this study (114). Many methods for measuring bruising are destructive in nature as they require penetration, piercing and cutting the tissue. Infrared

spectroscopy, hyperspectral imaging, thermal imaging and nuclear magnetic resonance imaging are cutting edge technologies that are non-destructive (115-118). However, after consideration, they are unproven technologies in dentistry, impractical for the oral cavity, exceeded study time constraints and/or cost prohibitive for this study.

Unlike pain and inflammation, significant bruising does not always accompany an oral surgical procedure. The bruising scale's purpose was to measure the degree and persistence of bruising in and around the site. In this study, the bruising score was based on self-report by the patient's daily survey observations as well as the investigator's perspective.

Intra-Oral Healing

Periapical surgery is an invasive procedure. There is no alternative to the process of gingival incisions and root resection. This process of removing unhealthy tissues and requires damaging the surrounding healthy tissue to access the root. The surgical wound can be a source of general discomfort during the recovery period (34).

Part of surgical wound assessment is wound measurement. Due to the variation in access points and severity of incisions, it was difficult to use a consistent technique among cases. Some patients were unable to retract their cheek and/or lips to evaluate the surgical site. In these instances, patients were asked not to evaluate their intraoral healing to avoid disruption of the sutured site.

Development of the Survey

The goal of the survey was to provide the patient with a document to record and collect data on their recovery experience. Pain, swelling, bruising (discoloration) and intra-oral healing (wound healing) are the four areas of recovery that the patient assessed (Figure 3). Factual information was included on the form such as date, coded patient identifier, investigator's name,

tooth type and the diagnosis.

The survey was created to be simple and easy to use. Although English literacy was required of patients for participation, minimal instructions with simple words were used in the document's instructions. Qualitative description of categories can impact how patients use the rating scale. For example, if only the points 1-6 are given without description, some might rarely select 6, whereas others may select the category often. If, instead, "6" is described as "near the maximum," the category is more likely to mean the same thing to different people. This could apply to all categories and not just the extreme points. Smiling and frowning emoticons were used instead of descriptive words to qualitatively characterize the scale and minimize the different interpretations. Although instructions were to be given to patients post-operatively when delivering the survey to the patient, it was created to be self-explanatory.

The likert scale type of question is arguably the most widely used response scale featured in surveys. It is often used to measure attitudes and other factors. The original scale featured five points. Over time, there have been many discussions and disagreements focused on what works best with the likert scale to give the most accurate responses. Most agree that more than seven points on a scale are too much. Studies show that people are not able to distinguish a scale greater than seven. Studies are not conclusive on which number scale is best.

The patients were instructed to complete the self-evaluation surveys on a likert-like visual analog scale for each of the post-operative categories of pain, swelling, bruising, and intra-oral healing. When responding to an item in this survey, patients were to indicate their rating by indicating a position along a continuous line between two end-points on a scale from 1 to 6 with "1" representing no symptoms and "6" representing the worst symptoms. Patients

made observations at four consecutive 24-hour intervals and recorded their experience on the survey. One week after the surgery, patients met with the investigator to submit their survey responses and complete a clinical evaluation.

At the one-week meeting, the principal investigators rated the patient's different healing categories. This allowed for verification of the magnitude of the patient's ratings. Ratings at the various time intervals allowed for the study of absolute levels of healing as well as the rates of recovery in the category over time.

Double-Blind Procedure

A blind experiment is an experiment technique in which information about the product or service that might lead to bias in the results is concealed from the parties involved until after the test. An open trial where such information is not concealed is vulnerable to such intentional or unconscious biases. The blind technique is used to eliminate human bias or influence of the study results.

A basic blind study would be an experiment where only the subject was unaware of information of the product or service being received. The person or investigator conducting the study would know beforehand which subjects were receiving which product or service. Researchers suggest that the person or investigator administering the experiment could influence the results of such studies by picking and choosing which subjects received which product or service. This would degrade the randomness of the study and could introduce bias.

If both tester and subject are blinded, the trial is a double-blind trial. A double-blind study requires that neither the subjects of the experiment nor the persons administering the experiment know the treatment assignments. This double-blind procedure is used to guard

against both experimenter bias and placebo effects. This study was performed under double-blind conditions.

The IDS at UNC provided control to ensure the double-blind conditions. Randomization of who received the drug or placebo injection was performed by the IDS. IDS also maintained custody of the syringes and were the only ones privy to who received which injections. Once notified of upcoming surgeries, IDS provided the identically prepared syringes the morning of the surgery. The identity of which patients received which injection was unknown to all operators, examiners, and resident surgeons and patients. Only after the completion of the treatments and examinations were the identities of the injections revealed.

Collection of Data

The collection of data in this study began with the initial consultation and concluded with the post-surgery evaluation.

Patients were scheduled to return one week after their surgical procedure with their completed survey. Photographs, clinical assessment and notations were made at the post-operative appointments by the principal investigator. There were two instances where the patients forgot to bring the survey document to their follow-up appointment. One patient sent the survey form to the investigator electronically and the other dictated survey form ratings verbally via telephone shortly after their appointment. Completed survey documents were stored in individual envelopes until the data analysis was initiated.

Upon completion of the surgical procedures, IDS was notified of the closing of the study. The information held by the IDS was then released to the principal investigator. At this point in time, the survey documents were unsealed and the tabulation of results began.

Analysis

Overview of General Statistics

All sixty patients completed their surgical procedures, completed their surveys and attended their post-operative evaluations. Upon conclusion of the study, the information held by the Investigational Drug Services was then released to the study's investigator. General statistics were compiled about the total sample and groups before the statistical methodology was applied and hypothesis testing began.

The total sample of the patients consisted of twenty-seven males and thirty-three females. The patients' ages were categorized as forty years old or under or forty-one and older. Fourteen were in the younger age group and forty-six were in the older age group. The race of the total sample included two of Asian descent, thirteen of African-American descent, six of Hispanic descent and thirty-nine of Caucasian descent (Table 4). The distribution of teeth that were treated included eight mandibular/anterior, thirteen mandibular/posterior, twenty-five maxillary/anterior and fourteen maxillary/posterior.

The demographics for the dexamethasone group included eleven males and nineteen females. The placebo group demographics of the selected patients were sixteen males and fourteen females (Table 1). The dexamethasone group distribution of age of the total sample were five were forty years old or under and twenty-five were age forty-one and older. The placebo group distribution of age of the total sample were nine were forty years old or under and twenty-one were age forty-one and older (Table 1).

The distribution of race that were treated in the dexamethasone group included one of Asian descent, seven of African-American descent, three of Hispanic descent and nineteen of Caucasian descent. The distribution of race that were treated in the placebo group included one

of Asian descent, six of African-American descent, three of Hispanic descent and twenty of Caucasian descent. Seven of the total sample patients were regular smokers of tobacco. Five of the thirty in the Dexamethasone Group were regular smokers of tobacco. Two of the thirty in the placebo group was regular smokers of tobacco.

The distribution of teeth that were treated in dexamethasone group included four mandibular/anterior, six mandibular/posterior, thirteen maxillary/anterior and seven maxillary/posterior. The distribution of teeth that were treated in placebo group included four mandibular/anterior, seven mandibular/posterior, twelve maxillary/anterior and seven maxillary/posterior.

Supportive Chi-square and Fisher's exact tests were performed to determine if the distribution of patients between the two groups was significantly different. The distribution of patients based on age, race, gender, tobacco users and teeth did not appear to be significantly different between the two groups. All p-values for the tests were $p>0.05$ which resulted in failure to reject the null hypothesis of equal proportions of patient personal characteristics and traits across treatment groups. This implies that IDS's randomization of patients provided a balanced and normal distribution of patients and their personal traits between the treatment groups.

Statistical Methodology

Parametric tests apply when data are continuous and normally distributed. The survey scale appears to be discrete (*i.e.,*1, 2, 3, 4, 5, 6) which means that it is not continuous. This would suggest that a non-parametric test would be the most appropriate. However, the survey scale is on a line with the numbered nodes. No instructions were given that the patient must rate according to a discrete scale. Patient number four made several fractional ratings during

the course of the survey. This casts doubt on the assumption that the patients view the scale as discrete, in which case a parametric test and assumption of continuous data may be more appropriate.

The statistical methodology employed to analyze the survey results and test the null hypothesis was the Pearson Chi-Squared test (χ^2). It is a goodness-of-fit statistical model that is often used and well known in the scientific research community. In order to avoid any perceived subtleties and fractions in the rating system, the rating from the surveys were grouped into two categories. The "Low" rating category was comprised of ratings 3 and below. The "High" rating category is comprised of ratings above 3.

The Pearson Chi-square test estimates or approximates how likely it is that an observed sampling distribution is due to chance. A Pearson Chi-square test is designed to analyze categorical data. In this study, analysis is of the High versus Low ratings of the patients that received dexamethasone versus the placebo. This test compares the observed data matrix to a matrix that distributes the data according to the expectation that the variables are independent. When observed data does not match expected data, the likelihood that the variables are dependent increases. With greater differences, the statistical significance increases. This increased significance can disprove the null hypothesis.

The Pearson Chi-square tests the null hypothesis (H_0) that the variables (ratings) are independent of the injection that the patient received. The Null Hypothesis in this Study is:

There is no statistically significant difference in postoperative complications with a single injection of dexamethasone versus a placebo at the time of periapical microsurgery.

H_0: $\mu_1 = \mu_2$

Where

H_0 = the null hypothesis,
μ_1 = the distribution of observed data, and
μ_2 = the distribution of expected data

If the null hypothesis is rejected, the alternative hypothesis must be accepted. The Alternative Hypothesis for this study is:

There is a reduction of postoperative complications with a single injection of dexamethasone at the time of periapical microsurgery compared to placebo injection.

Fisher's Exact Test is a statistical significance test that is often used and well known in scientific research community in the analysis of contingency tables. It examines the significance of the association (contingency) between two kinds of classification. It is most often used for categorical data that result from classifying objects in two different ways when the sample sizes are small. It derives its name as the P-value significance of the deviation from a null hypothesis calculated exactly rather than relying on an approximation by calculating table probabilities based on the hyper-geometric probability distribution.

Results

The survey ratings for the recovery categories of pain, swelling, bruising, intra-oral healing were analyzed individually. The following reviews the results of the individual categorical analysis.

A general statistical review of ranges and averages was performed first to assess the periodic ratings. This assisted in determining the likely statistic candidates for further statistical analysis. Pearson Chi-Squared test was applied to likely statistics to further assess correlations. In cases where statistical significance was found, a Fischer Exact Test was applied as a cross-check. As stated before, the ratings from the survey were grouped into high and low rating categories for each of the recovery categories at this stage.

Patients rated the pain that they experienced on the 6-point likert-like scale at 1 day, 2

days, 3 days, 4 days and 1 week after the procedure. The higher the pain level experienced, the higher the rating (Tables 2, 3).

Thirty-two of the sixty patients were symptomatic and were experiencing pain the day of the surgical procedure (Table 1). Those that received an injection of dexamethasone rated pain from 1 to 6 with an average rating of 2.5 and a standard deviation of 1.6 after twenty-four hours (Table 4). Those that received a placebo injection rated pain from 1 to 6 with an average rating of 3.2 and a standard deviation of 1.7. At forty-eight hours (two days), those that received an injection of dexamethasone rated pain from 1 to 5 with an average rating of 2.0 and a standard deviation of 1.3. Those that received a placebo injection rated pain from 1 to 6 with an average rating of 2.4 and a standard deviation of 1.4. At seventy-two hours, those that received an injection of dexamethasone rated pain from 1 to 5 with an average rating of 1.9 and a standard deviation of 1.3. Those that received a placebo injection rated pain from 1 to 6 with an average rating of 2.0 and a standard deviation of 1.2. At ninety-six hours, those that received an injection of Dexamethasone rated pain from 1 to 6 with an average rating of 1.6 and a standard deviation of 1.2. Those that received a placebo injection rated pain from 1 to 5 with an average rating of 1.6 and a standard deviation of 1.1. At the clinical evaluation appointment one week post-operatively, those that received an injection of dexamethasone rated pain from 1 to 5 with an average rating of 1.3 and a standard deviation of .9. Those that received a placebo injection rated pain from 1 to 3 with an average rating of 1.3 and a standard deviation of .7.

Patients rated the swelling that they experienced on the 6-point likert-like scale at 1 day, 2 days, 3 days, 4 days and 1 week after the procedure. The more swelling observed by the patient, the higher the rating (Table 2, 5).

Those that received an injection of dexamethasone rated swelling from 1 to 4 with an

average rating of 2.4 and a standard deviation of 1.0 after twenty-four hours (Table 6). Those that received a placebo injection rated swelling from 1 to 6 with an average rating of 3.1 and a standard deviation of 1.5. At forty-eight hours, those that received an injection of dexamethasone rated swelling from 1 to 5 with an average rating of 2.6 and a standard deviation of 1.1. Those that received a placebo injection rated swelling from 1 to 6 with an average rating of 3.1 and a standard deviation of 1.4. At seventy-two hours, those that received an injection of dexamethasone rated swelling from 1 to 5 with an average rating of 2.3 and a standard deviation of 1.2. Those that received a placebo injection rated swelling from 1 to 6 with an average rating of 2.5 and a standard deviation of 1.3. At ninety-six hours, those that received an injection of dexamethasone rated swelling from 1 to 4 with an average rating of 1.8 and a standard deviation of 1.0. Those that received a placebo injection rated swelling from 1 to 5 with an average rating of 1.9 and a standard deviation of 1.2. At the clinical evaluation appointment one week post-operatively, those that received an injection of dexamethasone rated swelling from 1 to 5 with an average rating of 1.3 and a standard deviation of 0.8. Those that received a placebo injection rated swelling from 1 to 3 with an average rating of 1.3 and a standard deviation of 0.5.

Observing the general statistic of range, average, rates of change and standard deviation of the ratings, the dexamethasone group appears to have performed similar the placebo group from day 2 and after. However, the day 1 average rating of 3.1 for the placebo group was significantly higher than the 2.4 for the dexamethasone group (Figure 5). This warrants further statistical analysis which has been done below.

The Pearson's Chi-square test was performed on the 2 x 2 matrix of high and low rating scores for the day 1 of swelling.

Actual Frequency Distribution			
	High Rating	Low Rating	Total
dexamethasone	4	26	30
placebo	12	18	30
Total Observations	16	44	60

Expected Frequency Distribution			
	High Rating	Low Rating	Total
Dexamethasone	8	22	30
placebo	8	22	30
Total Observations	16	44	60

The test was done at the level of significance of 5% (α): Level of significance = α = .05, or 5%. Given that the distribution table is a 2 x 2 matrix, the degrees of freedom is equal to one: Degrees of Freedom = $d_f = 1$.

The pertinent Chi-square values are as below:

α =	.5	.1	.05	.02	.01
1 d_f	.455	2.706	3.841	5.412	6.635
2d_f	1.386	4.605	5.991	7.824	9.210
3d_f	2.366	6.251	7.815	9.837	11.345

The Chi-square value of 3.841 is the benchmark that must be exceeded for the null hypothesis to be rejected (Figure 4). The Chi-square value calculated for the swelling ratings distribution was **5.455**.

As a confirmation, the Fischer Exact Test was performed. A one-tail test was performed in the following Fischer Exact Test formulation:

$$p = \frac{\binom{a+b}{a}\binom{c+d}{c}}{\binom{n}{a+c}} = \frac{(a+b)!\ (c+d)!\ (a+c)!\ (b+d)!}{a!\ \ b!\ \ c!\ \ d!\ \ n!}$$

Where,

a = high ratings for dexamethasone group observed
b = low ratings for dexamethasone group observed
c = high ratings for placebo group observed
d = low ratings for placebo group observed
n = total population of ratings

The resulting P-value from the Fischer Exact Test for day-one swelling ratings was equal to 0.0195.

Patients rated the bruising that they experienced on the 6-point likert-like scale at 1 day (24 hours), 2 days (48 hours), 3 days (72 hours), 4 days (96 hours) and 1 week after the procedure (Tables 2, 7). The more bruising and discoloration observed, the higher the rating.

Those that received an injection of dexamethasone rated bruising from 1 to 5 with an average rating of 1.7 and a standard deviation of 1.4 after twenty-four hours (one day) (Table 8). Those that received a placebo injection rated bruising from 1 to 6 with an average rating of 2.0 and a standard deviation of 1.4. At forty-eight hours (two days), those that received an injection of dexamethasone rated bruising from 1 to 6 with an average rating of 2.0 and a standard deviation of 1.5. Those that received a placebo injection rated bruising from 1 to 6 with an average rating of 2.0 and a standard deviation of 1.4. At seventy-two hours (three days), those that received an injection of dexamethasone rated bruising from 1 to 6 with an average rating of 2.0 and a standard deviation of 1.5. Those that received a placebo injection rated bruising from 1 to 6 with an average rating of 1.8 and a standard deviation of 1.2. At ninety-six hours (four days), those that received an injection of dexamethasone rated bruising from 1 to 6 with an average rating of 1.9 and a standard deviation of 1.4. Those that received a placebo injection rated bruising from 1 to 6 with an average rating of 1.8 and a standard

deviation of 1.3. At the clinical evaluation appointment one week post-operatively, those that received an injection of dexamethasone rated bruising from 1 to 6 with an average rating of 1.6 and a standard deviation of 1.1. Those that received a placebo injection rated bruising from 1 to 6 with an average rating of 1.4 and a standard deviation of 1.1.

Patients rated the intra-oral healing that they experienced on the 6-point likert-like scale at 1 day, 2 days, 3 days, 4 days and 1 week after the procedure (Tables 2, 9). The more trauma and damage tissue observed, the higher the rating. Ten of the patients were unable to provide ratings for intra-oral healing due to the sutures that were placed after the surgical procedure. There was concern that by opening their mouth to visually inspect the healing process, tearing of the sutured tissue would occur. Five patients from the dexamethasone group and five patients from the placebo group did not render ratings at one time interval or another during the ratings time period.

Those that received an injection of dexamethasone rated intra-oral healing from 1 to 5 with an average rating of 2.6 and a standard deviation of 1.3 after twenty-four hours (Table 10). Those that received a placebo injection rated intra-oral healing from 1 to 6 with an average rating of 3.3 and a standard deviation of 1.6. At forty-eight hours, those that received an injection of dexamethasone rated intra-oral healing from 1 to 5 with an average rating of 2.7 and a standard deviation of 1.3. Those that received a placebo injection rated intra-oral healing from 1 to 6 with an average rating of 2.8 and a standard deviation of 1.7. At seventy-two hours, those that received an injection of dexamethasone rated intra-oral healing from 1 to 5 with an average rating of 2.2 and a standard deviation of 1.2. Those that received a placebo injection rated intra-oral healing from 1 to 6 with an average rating of 2.5 and a standard deviation of 1.3. At ninety-six hours, those that received an injection of dexamethasone rated intra-oral healing from

1 to 5 with an average rating of 1.9 and a standard deviation of 1.1. Those that received a placebo injection rated intra-oral healing from 1 to 5 with an average rating of 2.0 and a standard deviation of 1.0. At the clinical evaluation appointment one week post-operatively, those that received an injection of dexamethasone rated intra-oral healing from 1 to 5 with an average rating of 1.6 and a standard deviation of 1.0. Those that received a placebo injection rated intra-oral healing from 1 to 4 with an average rating of 1.6 and a standard deviation of 0.7.

Observing the general statistic of range, average, rates of change and standard deviation of the ratings, the dexamethasone Group appears to have performed similar the placebo group from day 2 and after. However, the day 1 average rating of 3.3 for the placebo group was significantly higher than the 2.6 for the dexamethasone group. This warrants further statistical analysis which is performed below.

As with the analysis of swelling and inflammation, the Pearson's Chi-square test was performed on the 2 x 2 matrix of high and low rating scores for the day 1 of intra-oral healing.

Actual Frequency Distribution

	High Rating	Low Rating	Total
dexamethasone	6	19	25
placebo	12	13	25
Total Observations	18	32	50

Expected Frequency Distribution

	High Rating	Low Rating	Total
dexamethasone	9	16	25
placebo	9	16	25
Total Observations	18	32	50

The test was done at the level of significance of 5% (α): Level of significance = α = .05, or 5%. Given that the distribution table is a 2 x 2 matrix, the degrees of freedom is equal to one: Degrees of Freedom = $d_f = 1$.

The pertinent Chi-square values are as below:

α =	.5	.1	.05	.02	.01
1 d_f	.455	2.706	3.841	5.412	6.635
2d_f	1.386	4.605	5.991	7.824	9.210
3d_f	2.366	6.251	7.815	9.837	11.345

The Chi-square value of 3.841 is the benchmark that must be exceeded for the null hypothesis to be rejected. The Chi-square value calculated for the intra-oral healing ratings distribution was 3.125.

As a confirmation and since the Pearson Chi-square test was near the 10% level of significance, the Fischer Exact Test was performed. Like the test performed for swelling and inflammation, a one-tail test was performed in the following Fischer Exact Test formulation:

$$p = \frac{\binom{a+b}{a}\binom{c+d}{c}}{\binom{n}{a+c}} = \frac{(a+b)!\ (c+d)!\ (a+c)!\ (b+d)!}{a!\ \ b!\ \ c!\ \ d!\ \ n!}$$

Where,

a = high ratings for dexamethasone group observed
b = low ratings for dexamethasone group observed
c = high ratings for placebo group observed
d = low ratings for placebo group observed
n = total population of ratings

The resulting P-value from the Fischer Exact Test for day-one intra-oral healing ratings was equal to 0.0977.

Discussion

Patients were informed that they could take 500 mg of Tylenol and Vicodin 5/300 for pain relief if necessary. Most patients experience pain post-operatively in the first twenty-four

hours. This was expected since a glucocorticoid steroid is known for its recovery properties and not for its anesthetizing effects. Forty-three of the sixty patients used Tylenol and/or Vicodin during the first twenty-four hours post-operatively. This may render the resulting affects of dexamethasone on pain inconclusive.

This is further supported by observing the rates of change in ratings from one time interval to the next between dexamethasone versus the placebo. The placebo group experienced a greater average pain rating change from day 1 to day 2 than the dexamethasone group. The average pain rating for the placebo group decreased 0.83. The average pain rating for the dexamethasone group only decreased 0.52. The trend continued from day 2 to day 3. The average pain rating for the placebo group decreased 0.43. The average pain rating for the dexamethasone group only decreased 0.12.

Improvement stabilized at this point and the rate of change was similar for the change in ratings between day 3 and day 4. The average pain rating for the placebo group dropped 0.33. The average pain rating for the dexamethasone group decreased 0.30. And finally, the average pain rating for the placebo group decreased 0.30 from the 4^{th} day to the 1 week appointment. For the same corresponding period, the average pain rating for the dexamethasone group decreased a comparable 0.27.

A supportive observation of the rating system is the average absolute ratings and average rates of change provided for day 3 and 4 and at the 1 week time intervals were nearly the same for both groups. The effects of 4.0 mg injection of dexamethasone were expected to cease after approximately 36 to 48 hours. During this post-operative period, patients would experience an untreated recovery path and pain level. The strikingly similar rating scores and changes support the study's assumption that patients' subjective judgments in rating pain are

comparable. The standard deviation statistic at the various time intervals for each of the groups during this post-operative period is approximately one rating point. The expected variation in pain actually experienced by patient would likely account for most of the variance rather than significantly different subjective rating scales.

The swelling statistics on day 2 and after are consistent through the time intervals and quite similar. The subtle difference appears statistically insignificant. A supportive observation of the rating system is the average absolute ratings at the one week follow-up appointment. This was nearly the same for both groups and the principal investigator. At this point of the post-operative period, patients' swelling would have neared completion. The strikingly similar rating scores support the study's assumption that patients' subjective judgments in rating swelling are comparable.

In review of the bruising rating general statistic of range, average, rates of change and standard deviation of the ratings, the placebo group appears to have performed slightly better than the dexamethasone group. The statistics are consistent through the time intervals and quite similar. The subtle difference is statistically insignificant.

A supportive observation of the rating system is the average absolute ratings at the one week follow-up appointment. This was nearly the same for both groups and the investigator. At this point of the post-operative period, patients' bruising would have peaked and begun to subside. The strikingly similar rating scores support the study's assumption that patients' subjective judgments in rating bruising are comparable.

The intra-oral healing statistics on day 2 and after are consistent through the time intervals and quite similar. The subtle difference appears statistically insignificant. A supportive observation of the rating system is the average absolute ratings at the one week

follow-up appointment was nearly the same for both groups and the investigator. At this point of the post-operative period, patients' intra-oral healing would have neared completion. The strikingly similar rating scores support the study's assumption that patients' subjective judgments in rating intra-oral healing are comparable.

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CHAPTER 2: FORMATTED FOR THE JOURNAL OF ENDODONTICS

Abstract

Introduction: Substantial inflammation, bruising and pain have been an inevitable consequence of oral surgery. There is limited data on assessing post-operative complication following periapical microsurgery using injectable corticosteroids. The purpose of this prospective, double blind randomized clinical trial is to evaluate the short-term post-operative healing of endodontic periapical microsurgery following the local administration of dexamethasone.

Methods: Sixty patients received a single local submucosal injection of either 4.0 mg of dexamethasone or a placebo saline solution at the conclusion of a standardized periapical microsurgery. A self-administered survey provided data for analytical comparison. Data was analyzed at a significance level of p=.05 using Chi square and Fisher's Exact tests.

Results: Subjects who received the dexamethasone injection reported less swelling 24 hours post-periapical microsurgery compared to the placebo with a statistically significant result of $p < .02$. Improvements in pain, bruising and intra-oral healing were not statistically significant.

Conclusions: This study demonstrated that a single submucosal low-dosage dexamethasone injection following periapical microsurgery reduces swelling at 24 hours post-operatively and can potentially lessen post-operative sequela.

Key Words: Apicoectomy, Endodontic Microsurgery, Inflammation, Corticosteroids, Dexamethasone, Outcome

Introduction

Initial endodontic therapy does not produce an acceptable treatment outcome in approximately one-third of all cases and results in the need for endodontic retreatment (1). In an analysis of surgical and non-surgical retreatment therapies (2), research shows that healing rates are not substantially different between the two approaches (3).

Periapical surgery is regarded as an integral part of modern endodontics (4, 5). Endodontic surgeries account for approximately 6 to 10% of the typical endodontic practice treatments (6, 7) and are considered an extension of non-surgical treatments. Based on short and long term evaluations, periapical surgeries have a 91 to 97% healing success rate (8, 9) making periapical microsurgery a good treatment option. Research indicates that substantial inflammation, pain, and bruising have long been an inevitable consequence of oral surgery (10). The anti-inflammatory efficacy of corticosteroids has led to their extensive use after surgical procedures (11-14). Dexamethasone has been successful in reducing the post-operative sequelae (8, 11-21), edema, and inflammation that typically accompany oral surgery. Endodontic microsurgery studies have shown some success using oral dexamethasone both preoperatively and postoperatively (15, 20, 21). One endodontic surgical model suggested that the routine use of oral dexamethasone is a safe method to reduce pain and swelling after endodontic surgery (8). However, no post-operative symptoms were analyzed in that model. The purpose of this double blind randomized clinical study is to evaluate short-term post-operative healing of endodontic microsurgery using a 4.0 mg local submucosal injection of the dexamethasone at the conclusion of periapical microsurgery.

Materials and Methods

Sixty adult patients (27 men and 33 women) participated in this study (Table 1). All participants were in good health as verified by the health history questionnaire and examination. Criteria for inclusion were as follows: relatively healthy adult participants 18 years of age or older without chronic pain conditions or underlying chronic systemic conditions. All teeth with persistent endodontic lesions after retreatment or initial root canal therapy where retreatment is not possible (post, anatomy, iatrogenic complications) were eligible. Exclusion criteria: (1) Miller Class III/IV mobility, (2) compromised crown to root ratio, (3) combined endodontic-periodontic lesions, (4) chronic pain, (5) systemic medical conditions, (6) pregnancy, (7) allergy to dexamethasone, (8) allergy to local anesthetics or sulfites, (9) younger than 18 years of age, (10) acute systemic conditions. The University of North Carolina at Chapel Hill (UNC) Institutional Review Board (IRB) approved the study (IRB protocol number 13-2336). Written and informed consents were obtained from each patient prior to a surgical intervention.

Using a double-blind randomized controlled setting, the 60 patients were randomly assigned to the intervention (4.0 mg of dexamethasone) or placebo (saline solution) groups with 30 patients in each group. Randomization was performed by the Investigational Drug Services (IDS protocol number 2519) at the UNC hospital. Patients were required to have three appointments. The first appointment was a screening appointment to review the medical history, clinical and radiographic evaluation to determine qualification. If a patient qualified for the study, the next appointment was the periapical microsurgery. Lastly, the patient returned for the one week follow-up appointment post-operatively.

With the exception of incisions and suturing, all microsurgical procedures were performed using a Surgical Operating Microscope (Global G6 Microscope, Global Surgical Corporation, St. Louis, MO) using modern microsurgical techniques. After profound anesthesia with 2% Lidocaine with 1:100,000/1:50,000 of epinephrine, a split-thickness papilla-base muco-periosteal flap was used to ensure standardization and to allow for the most esthetic outcome. If necessary, osteotomies were performed using a #6 round carbide bur in a high-speed impact air hand piece (Sybron Endo, USA) under copious water irrigation. A curettage of granulation/pathological tissue was performed and tissues were submitted to the UNC Department of Pathology for histological analysis. A resection of apical 3 mm of the root performed with 0-30% bevel. The resected surface of the root was stained with methylene blue dye (Vista BLUE, VISTA Dental Products, USA) and inspected under a microscope using a micro-mirror to detect any cracks, fractures, dentinal defects or missed anatomy. The root-end preparation was performed at least 3.0 mm into the canal space following the long axis of the tooth using ultrasonic surgical tips (Obtura, Spartan) under saline irrigation. Mineral trioxide aggregate (MTA – Angelus Dental Solutions, Londrina, Parana, Brazil) was used as a root-end filling material and placed into the root-end preparation using the micro-apical-placement system (MAP by Roydent Dental Products, Switzerland). The soft-tissues were approximated and primary closure was achieved with 5.0 and 4.0 chromic gut sutures. A local submucosal injection of dexamethasone 4.0 mg or placebo saline solution was then placed at the conclusion of the surgery.

Irrespective of the group assigned, patients received the same standard post-operative care instructions in verbal and written form. All participants were given a standard post-operative surgery prescription for pain control for the following three days to be taken if

needed. The prescription included 12 tablets each of Tylenol 500 mg and Vicodin 3/500. Participants were advised to take both tablets every 6 hours if they experienced pain while not taking more than 4 dosages in a 24 hour period.

All patients were provided with a take-home survey to record their pain, swelling, external bruising, and intra-oral healing recovery on a Likert-like 6 point visual analog scale at 24, 48, 72, 96 hours and at day 7. The 6 point visual analog had a continuous line that ranged from 1 to 6 with "1" being no symptoms and "6" being severe symptoms (Figure 3). Patients were instructed to record the amount of pain medication consumed on the survey form. Upon return for the one-week follow-up appointment, the primary investigator used the same survey form to rate the same post-operative recovery categories.

In order to ensure standardization, endodontic residents (second and third year graduate endodontic residents at UNC School of Dentistry) performed all of the periapical microsurgeries. Prior to participation in this study, each endodontic resident had previously performed at least forty endodontic surgeries. Besides having been trained in the same endodontic program, all participating endodontic residents attended a 6-hour lecture and watched a video on the standardized surgical procedures prior to the study. In addition to this calibration and standardization, the principal investigator either performed or assisted in all of the research surgeries. In order to avoid variances or errors during each procedure, the principal investigator, when not performing research surgery, was assisting in order to verify accurate papilla-base flap design and flap reflection; standardized osteotomies, curettage, root-end resection, root end-preparation and the placement of MTA (confirmed with a radiograph), and suturing. The primary investigator performed the injections at the conclusion of each surgery. All of the residents and the patients that were participating in the

study were informed that the principal investigator could intervene at any point during the surgery in order to be consistent with the protocol. Only the principal investigator performed the follow-up evaluations for uniformity of the results.

Upon completion of the study, the data was statistically analyzed. Randomization of patient group assignment was performed by IDS. The proportions of each group's gender, age of subjects, tobacco use, or race, or tooth type were assessed by using the randomization test as a cross-check. Correlation tests between the ratings and the demographic traits were tested using the Mantel-Haenszel test (Table 2).

A 2 x 2 matrix distribution table was created of high and low ratings of each group. The Pearson Chi-square is used to test the difference in recovery ratings. A two-tailed test with no corrections was utilized. The test was done at the level of significance of p-value = .05 with one degree of freedom. A normal and continuous distribution was confirmed and used in the test. In instance where statistical significance was calculated, it was confirmed with the one-tailed Fischer Exact Test.

Results

There was no statistically significant difference between the two group's participants based on gender, age of subjects, tobacco use, or race, or tooth type ($p>.05$) (Table 2). After 48 hours, the pain, swelling, bruising and intraoral healing ratings by the two groups were practically indistinguishable with even general statistics (Tables 2, 4, 6, 8, 10). The greatest statistical difference occurs at 24 hours post-operatively for each category.

There was no statistically significant difference between the two group's pain and bruising ratings at any time interval. At 24 hours post-operatively, the intraoral healing achieved it greatest significance narrowly missing the statistically significance benchmark

(3.125 < 3.841). The Fischer Exact Test was performed and supported this result with a p=.0977.

At the same point in time, the swelling improvement not only exceeds the benchmark (5.455 > 3.841), but the p-value = .02 mark as well (5.455 > 5.412). The Fischer Exact Test was performed and confirmed the result with a p=.0195 which translates to more than 98% confidence.

Discussion

This study shows that a dexamethasone injection may reduce some post-operative sequelae. The effect of dexamethasone was most pronounced with a reduction of swelling at 24-hours post-operatively, the time at which swelling usually peaks. This study's data on swelling is consistent with the results of other studies in the oral surgery literature (14, 16, 17, 19, 20). No statistically significant correlations were found between gender, age of subjects, tobacco use, or race, or tooth type versus recovery ratings. This study's finding that the efficacy of dexamethasone in the maxilla and mandible was similar and is supported by other research that found dexamethasone is absorbed from the injection site and distributes between both maxilla and mandible similarly (22).

This study used a very conservative single 4.0 mg dexamethasone dosage to ensure a safe, effective and efficient dosage. Corticosteroids at higher levels with multiple dosages have been found to cause adrenal fatigue and can mask symptoms of bacterial infection (23). This study's dosage level of dexamethasone and its expected duration of action does not suppress the adrenal glands and, therefore, does not pose any risk of stress intolerance. Research has shown that a one-week course of corticosteroids is not only safe, but very effective in reducing post-surgical dental pain and swelling (23). An important finding of that

study was that patients required less NSAIDs and narcotics to control their post-operative pain. A single dose of corticosteroids has also been proven to be safe and effective in terms of reducing pain and swelling by other research (24). A study by Czerwinski concluded that a single large intravenous dose of dexamethasone (2.0 milligrams per kilogram of body weight) does not have any harmful side effects (24). This instance study used a single small dose of 4.0 mg of dexamethasone (17) which is much less than what was used in the Czerwinski study. Previous studies found that a single local submucosal injection of 4.0 mg of dexamethasone was proven to be as effective as 8.0 mg in reducing post-operative complications (17).

This study utilized a smaller dosage of dexamethasone in order to minimize potential side effects. A single dose of corticosteroid at this low level has no harmful effects (24). Some research suggests giving corticosteroids pre-operatively (11, 12, 14) in consideration of the delayed therapeutic effect (25-27). It is suggested that dexamethasone may inhibit the initial step of the inflammatory cascade (28). It is further suggested that an injectable form of corticosteroids may induce a more rapid affect (29) than if dexamethasone is taken orally. While the oral administration of dexamethasone is convenient and clinically effective (11, 21), patient compliance and the need for repeated doses to sustain adequate steroid concentration can become problematic with oral administration. It is more predictable and effective to inject the dexamethasone at the time of the surgery rather than using the oral route.

There is little formal conformation of dexamethasone's efficacy in controlled studies. Previous research has provided inconsistent results due to the lack of uniformity in study design and varying measurement techniques. Recommended dosage and routes of dexamethasone administration have varied as well. One oral surgery study failed to show any

significant improvement in swelling and pain following treatment with a 4.0 mg oral dose of dexamethasone (14). However, other research has shown significant swelling reduction with 8.0 mg of dexamethasone taken orally (19). Furthermore, other oral surgery research has shown that 4.0 mg of dexamethasone injected submucosally had the same efficacy as 8.0 mg in reducing swelling 24-hours post-operatively (17). That same study failed to demonstrate any impact on pain using both doses of dexamethasone. Another endodontic surgery study suggests administering corticosteroids routinely afterwards to prevent swelling and pain and is described as an effective and safe method (8). However, post-operative symptoms were not analyzed by that particular study. Other traditional periapical surgery research reported swelling and pain in all patients undergoing treatment although no steps were taken to prevent swelling (10).

Patients self-assessed their pain, swelling, bruising, and intra-oral healing on a commonly accepted visual analog scale used in dental and medical research (30, 31). Each patient rated and recorded the degree of the pain, swelling, bruising and intra-oral healing (when possible) at day 1, 2, 3, 4 and 7. The scale ranged from 1 to 6 where "1" referred to no symptoms and "6" referred to severe symptoms. Visual analogs scores are commonly combined during the statistical analysis (32, 33). In this study, some intra-oral healing rates were not recorded by patients due to the risk of suture tearing. This study combined scores of less than 3 in the "low" rating category and scores of more than 3 in a "high" rating category.

There was no statistically significant difference in this study between the dexamethasone group and the placebo group for the pain and bruising categories at any point in time (Figure 6). The failure to reduce pain is consistent with other oral surgery research

findings (17, 19, 21). Pre-operative symptoms did not significantly alter pain ratings for either group in this study contrary to previous studies (15, 34).

The only statistically significant improvement was in the swelling recovery category of the dexamethasone group compared to the placebo group at 24 hours post-operatively. The recovery category "intraoral healing" category narrowly missed the statistically significant benchmark ($p<0.05$) at 24 hours post-operatively. It appears that the anti-inflammatory effect of 4.0 mg submucosal dexamethasone is either minimal after 24 hours or an insufficient dosage was administered to observe a more pronounced improvement later than 24 hours.

Routine antibiotics were not prescribed since no patients exhibited symptoms of malaise or fever. This protocol is supported by a study that found that routine antibiotic therapy is not necessary at the time of oral surgery with the use of corticosteroids (21, 35). Antibiotics were only prescribed in two instances in this study where exposure of the maxillary sinus occurred during the surgical procedure; one patient was in the dexamethasone group and the other patient was in the placebo group. The use of antibiotics did not impact the results as patients were split between the groups.

In conclusion, this study demonstrated that a single low-dose submucosal dexamethasone injection minimizes swelling 24 hours following periapical microsurgery and can potentially lessen post-operative sequela. Future comparative studies are needed in this field to establish a protocol on reducing post-operative complications.

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Table 1

Case Distribution		
	Dexamethasone	Placebo
Sex:		
Females	19	14
Males	11	16
Age:		
40 and Under	5	9
Over Age 40	25	21
Tooth Type:		
Anterior / Mandibular	4	4
Anterior / Maxillary	13	12
Posterior / Mandibular	6	7
Posterior / Maxillary	7	7
Race:		
Asian	1	1
African American	7	6
Hispanic	3	3
Caucasian	19	20
Tobacco:		
User	5	2
Non - User	25	28
Symptomatic Day of Surgery:		
Displays Symptoms	18	14
No Symptoms	12	16

Table 2

Summary of Pain, Swelling, Bruising, Intra-Oral Healing by High and Low Ratings

	Dexamethasone			Placebo			
	Low Ratings	High Ratings	Total	Low Ratings	High Ratings	Total	P-Value
Day 1:							
Pain	21	9	30	16	14	30	0.1843
Swelling	26	4	30	18	12	30	0.0195
Bruising	26	4	30	25	5	30	0.7177
Intra-Oral	19	6	25	13	12	25	0.0771
Day 2:							
Pain	25	5	30	23	7	30	0.5186
Swelling	22	8	30	19	11	30	0.4051
Bruising	25	5	30	26	4	30	0.7177
Intra-Oral	17	8	25	17	9	26	0.8430
Day 3:							
Pain	25	5	30	26	4	30	0.7177
Swelling	23	7	30	26	4	30	0.3169
Bruising	24	6	30	27	3	30	0.2781
Intra-Oral	22	3	25	20	6	26	0.2996
Day 4:							
Pain	27	3	30	26	4	30	0.6876
Swelling	28	2	30	26	4	30	0.3894
Bruising	26	4	30	26	4	30	1.0000
Intra-Oral	23	2	25	24	2	26	0.2996
1 Week:							
Pain	28	2	30	30	0	30	0.1503
Swelling	29	1	30	30	0	30	0.3132
Bruising	29	1	30	29	1	30	1.0000
Intra-Oral	24	1	25	25	1	26	0.9674

Table 3
Page 1 of 2

Patient Survey Ratings for Pain - Raw Data

Patient Number	Treatment	Pain Ratings					
		1 Day	2 Days	3 Days	4 Days	1 week	Investigator
1	Dexamethasone	1	1	1	1	1	1
2	Placebo	2	1	1	1	1	1
3	Placebo	1	1	1	1	1	1
4	Dexamethasone	2	1.5	1	1	1	1
5	Dexamethasone	1	1	1	1	1	1
6	Placebo	1	1	1	1	1	1
7	Placebo	2	1	1	1	1	1
8	Dexamethasone	4	3	3	3	1	1
9	Dexamethasone	1	1	1	1	1	1
10	Placebo	2	3	2	1	1	1
11	Placebo	3	3	2	1	1	1
12	Dexamethasone	3	1	2	1	1	1
13	Dexamethasone	2	1	1	1	1	1
14	Placebo	2	2	2	2	1	1
15	Dexamethasone	5	4	5	1	1	1
16	Dexamethasone	1	1	1	1	1	1
17	Placebo	5	3	2	1	1	1
18	Placebo	1	1	1	1	1	1
19	Placebo	3	2	1	1	1	1
20	Placebo	5	4	3	2	1	2
21	Placebo	4	2	2	1	1	1
22	Dexamethasone	1	1	1	1	1	1
23	Dexamethasone	1	1	1	1	1	1
24	Dexamethasone	3	2	1	1	1	1
25	Dexamethasone	1	1	1	1	1	1
26	Placebo	5	1	1	2	1	1
27	Dexamethasone	1	1	1	1	1	1
28	Dexamethasone	4	1	1	1	1	1
29	Placebo	5	2	1	1	1	1
30	Placebo	5	4	4	4	2	2

Table 3
Page 2 of 2

Patient Survey Ratings for Pain - Raw Data

Patient Number	Treatment	Pain Ratings					
		1 Day	2 Days	3 Days	4 Days	1 week	Investigator
31	Placebo	3	2	2	1	1	1
32	Placebo	1	1	1	1	1	1
33	Placebo	1	1	1	1	1	1
34	Dexamethasone	4	5	5	4	2	1
35	Dexamethasone	1	1	1	1	1	1
36	Dexamethasone	4	4	4	6	4	2
37	Dexamethasone	1	3	3	2	1	1
38	Placebo	5	4	2	2	1	1
39	Dexamethasone	1	1	1	1	1	1
40	Placebo	6	6	6	5	3	1
41	Placebo	4	3	4	4	3	1
42	Dexamethasone	1	1	1	1	1	1
43	Dexamethasone	3	2	2	1	1	1
44	Placebo	5	3	2	1	1	1
45	Placebo	4	4	4	4	3	1
46	Placebo	1	1	1	1	1	1
47	Dexamethasone	6	5	4	2	1	1
48	Dexamethasone	5	2	1	1	1	1
49	Dexamethasone	5	4	3	2	2	2
50	Placebo	6	5	2	2	2	2
51	Dexamethasone	3	3	2	2	1	1
52	Dexamethasone	1	1	1	1	1	1
53	Placebo	1	1	1	1	1	1
54	Placebo	4	2	1	1	2	1
55	Placebo	5	4	3	2	2	2
56	Dexamethasone	5	3	4	4	5	2
57	Dexamethasone	3	2	1	1	1	1
58	Placebo	2	2	2	1	1	1
59	Dexamethasone	1	1	1	1	1	1
60	Placebo	3	2	2	1	1	1

Table 4

General Statistics of the Dexamethasone and Placebo Group's Pain Ratings			
	Average Rating	Range	Standard Deviation
Dexamethasone :			
Day 1 / 24 Hours	2.5	1 to 6	1.6
Day 2 / 48 Hours	2.0	1 to 5	1.3
Day 3 / 72 Hours	1.9	1 to 5	1.3
Day 4 / 96 Hours	1.6	1 to 6	1.2
1 week	1.3	1 to 5	0.9
Investigator's Rating at 1 week appointment	1.1	1 to 2	0.3
Placebo :			
Day 1 / 24 Hours	3.2	1 to 6	1.7
Day 2 / 48 Hours	2.4	1 to 6	1.4
Day 3 / 72 Hours	2.0	1 to 6	1.2
Day 4 / 96 Hours	1.6	1 to 5	1.1
1 week	1.3	1 to 3	0.7
Investigator's Rating at 1 week appointment	1.1	1 to 2	0.3

Table 5
Page 1 of 2

Patient Survey Ratings for Swelling - Raw Data

Patient Number	Treatment	Swelling Ratings					
		1 Day	2 Days	3 Days	4 Days	1 week	Investigator
1	Dexamethasone	1	1	1	1	1	1
2	Placebo	2	1	1	1	1	1
3	Placebo	1	1	1	1	1	1
4	Dexamethasone	3	3	3	2	1	1
5	Dexamethasone	2	2	1	1	1	1
6	Placebo	1	1	1	1	1	1
7	Placebo	2	2	2	1	1	1
8	Dexamethasone	4	4	3	3	1	1
9	Dexamethasone	2	4	3	2	1	1
10	Placebo	1	3	2	3	1	1
11	Placebo	3	4	3	1	1	1
12	Dexamethasone	2	1	2	1	1	1
13	Dexamethasone	3	2	1	1	1	1
14	Placebo	1	2	2	2	2	1
15	Dexamethasone	3	4	5	1	1	1
16	Dexamethasone	2	2	1	1	1	1
17	Placebo	4	5	3	1	1	1
18	Placebo	3	3	3	3	2	1
19	Placebo	5	4	3	2	1	3
20	Placebo	4	3	2	1	1	1
21	Placebo	4	5	3	2	1	1
22	Dexamethasone	1	2	1	1	1	1
23	Dexamethasone	1	2	3	2	1	1
24	Dexamethasone	2	3	1	1	1	1
25	Dexamethasone	2	2	2	1	1	1
26	Placebo	5	4	1	1	1	1
27	Dexamethasone	2	2	2	2	2	2
28	Dexamethasone	3	5	4	3	2	2
29	Placebo	3	2	1	1	1	1
30	Placebo	4	4	4	4	2	2

Table 5
Page 2 of 2

Patient Survey Ratings for Swelling - Raw Data

Patient Number	Treatment	Swelling Ratings					
		1 Day	2 Days	3 Days	4 Days	1 week	Investigator
31	Placebo	4	6	6	4	2	2
32	Placebo	5	4	3	2	1	1
33	Placebo	2	2	2	1	1	1
34	Dexamethasone	3	4	4	4	1	1
35	Dexamethasone	3	4	4	3	1	1
36	Dexamethasone	4	4	4	4	1	1
37	Dexamethasone	2	4	4	3	2	1
38	Placebo	2	2	2	1	1	1
39	Dexamethasone	3	2	1	1	2	1
40	Placebo	6	6	6	5	2	1
41	Placebo	3	2	2	2	1	1
42	Dexamethasone	1	1	1	1	1	1
43	Dexamethasone	3	3	2	2	1	1
44	Placebo	2	2	1	1	1	1
45	Placebo	3	3	5	4	3	1
46	Placebo	5	4	2	1	1	2
47	Dexamethasone	1	3	4	2	1	1
48	Dexamethasone	3	2	1	1	1	1
49	Dexamethasone	4	3	2	2	1	1
50	Placebo	6	5	3	3	2	1
51	Dexamethasone	3	3	2	2	1	1
52	Dexamethasone	1	1	1	1	1	1
53	Placebo	2	2	2	1	1	1
54	Placebo	4	3	3	2	2	1
55	Placebo	3	3	3	3	1	2
56	Dexamethasone	2	2	2	3	5	5
57	Dexamethasone	4	3	2	1	1	1
58	Placebo	2	2	2	1	1	1
59	Dexamethasone	2	1	1	1	1	1
60	Placebo	2	2	2	1	1	1

Table 6

General Statistics of the Dexamethasone and Placebo Group's Swelling Ratings

	Average Rating	Range	Standard Deviation
Dexamethasone :			
Day 1 / 24 Hours	2.4	1 to 4	1.0
Day 2 / 48 Hours	2.6	1 to 5	1.1
Day 3 / 72 Hours	2.3	1 to 5	1.2
Day 4 / 96 Hours	1.8	1 to 4	0.9
1 week	1.3	1 to 5	0.8
Investigator's Rating at 1 week appointment	1.2	1 to 5	0.7
Placebo :			
Day 1 / 24 Hours	3.1	1 to 6	1.5
Day 2 / 48 Hours	3.1	1 to 6	1.4
Day 3 / 72 Hours	2.5	1 to 6	1.3
Day 4 / 96 Hours	1.9	1 to 5	1.2
1 week	1.3	1 to 3	0.5
Investigator's Rating at 1 week appointment	1.2	1 to 3	0.5

Table 7
Page 1 of 2

Patient Survey Ratings for Bruising - Raw Data

Patient Number	Treatment	Bruising					
		1 Day	2 Days	3 Days	4 Days	1 week	Investigator
1	Dexamethasone	1	1	1	1	1	1
2	Placebo	1	1	1	1	1	1
3	Placebo	1	1	1	1	1	1
4	Dexamethasone	1	3	3	3	1.5	2
5	Dexamethasone	1	1	1	1	1	1
6	Placebo	1	1	1	1	1	1
7	Placebo	1	1	1	1	1	1
8	Dexamethasone	1	1	1	1	1	1
9	Dexamethasone	5	5	5	3	2	1
10	Placebo	1	1	1	1	1	1
11	Placebo	2	2	1	1	1	1
12	Dexamethasone	3	1	1	1	1	1
13	Dexamethasone	1	1	1	1	1	1
14	Placebo	4	4	3	3	2	1
15	Dexamethasone	1	1	1	1	1	1
16	Dexamethasone	1	2	2	1	1	1
17	Placebo	4	2	1	1	1	1
18	Placebo	2	2	2	2	1	1
19	Placebo	3	3	2	1	1	1
20	Placebo	1	1	1	2	1	1
21	Placebo	1	2	2	1	1	1
22	Dexamethasone	1	1	1	1	1	1
23	Dexamethasone	1	1	1	2	1	1
24	Dexamethasone	1	1	1	1	1	1
25	Dexamethasone	1	1	1	1	1	1
26	Placebo	1	1	1	1	1	1
27	Dexamethasone	3	2	2	2	1	1
28	Dexamethasone	1	3	4	4	3	3.5
29	Placebo	2	2	1	1	1	1
30	Placebo	3	3	2	2	1	1

Table 7
Page 2 of 2

Patient Survey Ratings for Bruising - Raw Data

Patient Number	Treatment	Bruising					
		1 Day	2 Days	3 Days	4 Days	1 week	Investigator
31	Placebo	4	5	3	2	2	1
32	Placebo	1	1	1	1	1	1
33	Placebo	1	1	1	1	1	1
34	Dexamethasone	1	1	1	1	1	1
35	Dexamethasone	1	2	4	4	2	3
36	Dexamethasone	1	1	1	1	1	1
37	Dexamethasone	1	5	5	5	3	3
38	Placebo	1	1	1	1	1	1
39	Dexamethasone	3	2	1	1	1	1
40	Placebo	6	6	6	5	1	1
41	Placebo	1	1	1	1	1	1
42	Dexamethasone	1	1	1	1	1	1
43	Dexamethasone	4	3	3	2	2	1
44	Placebo	1	1	1	1	1	1
45	Placebo	1	1	2	4	3	1
46	Placebo	1	1	2	2	1	1
47	Dexamethasone	1	1	1	1	1	1
48	Dexamethasone	1	1	1	1	1	1
49	Dexamethasone	5	5	4	3	3	2
50	Placebo	1	2	4	6	3	3
51	Dexamethasone	1	1	1	1	1	1
52	Dexamethasone	1	6	6	6	6	3
53	Placebo	2	2	2	1	1	1
54	Placebo	5	5	4	4	6	3
55	Placebo	3	3	1	2	2	2
56	Dexamethasone	1	2	2	1	2	3
57	Dexamethasone	5	4	3	3	2	2
58	Placebo	2	2	2	2	2	2
59	Dexamethasone	1	1	1	1	1	1
60	Placebo	1	1	1	1	1	1

Table 8

General Statistics of the Dexamethasone and Placebo Group's Bruising Ratings

	Average Rating	Range	Standard Deviation
Dexamethasone :			
Day 1 / 24 Hours	1.7	1 to 5	1.3
Day 2 / 48 Hours	2.0	1 to 6	1.5
Day 3 / 72 Hours	2.0	1 to 6	1.5
Day 4 / 96 Hours	1.9	1 to 6	1.4
1 week	1.6	1 to 6	1.1
Investigator's Rating at 1 week appointment	1.5	1 to 3.5	0.8
Placebo :			
Day 1 / 24 Hours	2.0	1 to 6	1.4
Day 2 / 48 Hours	2.0	1 to 6	1.4
Day 3 / 72 Hours	1.8	1 to 6	1.2
Day 4 / 96 Hours	1.8	1 to 6	1.3
1 week	1.4	1 to 6	1.0
Investigator's Rating at 1 week appointment	1.2	1 to 3	0.5

Table 9
Page 1 of 2

Patient Survey Ratings for Intra-Oral Healing - Raw Data

Patient Number	Treatment	Intra-Oral Healing Ratings					
		1 Day	2 Days	3 Days	4 Days	1 week	Investigator
1	Dexamethasone	1	1	1	1	1	1
2	Placebo	2	1	1	1	1	2
3	Placebo	1	1	1	1	1	1
4	Dexamethasone	4	3.5	3	2.5	1.5	1
5	Dexamethasone	4	4	3	1	1	1
6	Placebo	1	1	1	1	1	1
7	Placebo	1	1	1	1	1	2
8	Dexamethasone	5	5	3	3	3	2
9	Dexamethasone	4	4	3	2	2	2
10	Placebo	2	2	2	2	2	2
11	Placebo	6	6	4	3	2	2
12	Dexamethasone	3	1	1	1	1	2
13	Dexamethasone	2	2	2	1	1	1
14	Placebo	5	4	3	3	2	1
15	Dexamethasone	3	3	1	1	1	2
16	Dexamethasone	1	1	1	1	1	1
17	Placebo	5	5	4	3	1	2
18	Placebo	3	2	2	2	1	1
19	Placebo	4	3	3	2	2	3
20	Placebo	5	4	4	2	1	2
21	Placebo	3	3	3	2	2	2
22	Dexamethasone	1	2	1	1	1	1
23	Dexamethasone	2	3	3	2	1	2
24	Dexamethasone	1	1	1	1	1	2
25	Dexamethasone	3	3	1	1	1	2
26	Placebo	2	1	1	1	1	2
27	Dexamethasone	3	2	2	2	1	1
28	Dexamethasone	3	4	4	3	3	3
29	Placebo	2	1	1	1	1	1.5
30	Placebo	NR	NR	NR	NR	NR	2

Table 9
Page 2 of 2

Patient Survey Ratings for Intra-Oral Healing - Raw Data

Patient Number	Treatment	Intra-Oral Healing Ratings					
		1 Day	2 Days	3 Days	4 Days	1 week	Investigator
31	Placebo	4	4	3	2	2	3
32	Placebo	4	3	3	2	2	2
33	Placebo	2	1	1	1	1	2
34	Dexamethasone	1	2	3	2	2	1
35	Dexamethasone	1	1	1	1	1	1
36	Dexamethasone	2	2	2	2	2	2
37	Dexamethasone	3	4	4	4	3	3
38	Placebo	4	3	2	1	1	2
39	Dexamethasone	3	2	1	1	1	2
40	Placebo	6	6	6	5	2	2
41	Placebo	4	4	4	2	2	3
42	Dexamethasone	1	1	1	1	1	1
43	Dexamethasone	4	4	3	2	1	3
44	Placebo	NR	NR	NR	NR	NR	1
45	Placebo	NR	2	3	4	4	2
46	Placebo	4	4	3	2	1	1
47	Dexamethasone	NR	NR	NR	NR	NR	1
48	Dexamethasone	NR	NR	NR	NR	NR	3
49	Dexamethasone	NR	NR	NR	NR	NR	3
50	Placebo	3	3	3	3	2	3
51	Dexamethasone	3	3	3	2	1	1
52	Dexamethasone	5	5	5	5	5	3
53	Placebo	1	1	1	1	1	2
54	Placebo	6	6	4	3	3	3
55	Placebo	NR	NR	NR	NR	NR	2
56	Dexamethasone	3	3	3	3	3	3
57	Dexamethasone	NR	NR	NR	NR	NR	3
58	Placebo	2	2	2	2	2	2
59	Dexamethasone	NR	NR	NR	NR	NR	2
60	Placebo	NR	NR	NR	NR	NR	1

NR = No Rating

Table 10

General Statistics of the Dexamethasone and Placebo Group's Intra-Oral Healing Ratings

	Average Rating	Range	Standard Deviation
Dexamethasone :			
Day 1 / 24 Hours	2.6	1 to 5	1.3
Day 2 / 48 Hours	2.7	1 to 5	1.3
Day 3 / 72 Hours	2.2	1 to 5	1.2
Day 4 / 96 Hours	1.9	1 to 5	1.1
1 week	1.6	1 to 5	1.0
Investigator's Rating at 1 week appointment	1.9	1 to 3	0.8
Placebo :			
Day 1 / 24 Hours	3.3	1 to 6	1.6
Day 2 / 48 Hours	2.8	1 to 6	1.7
Day 3 / 72 Hours	2.5	1 to 6	1.3
Day 4 / 96 Hours	2.0	1 to 5	1.0
1 week	1.6	1 to 4	0.7
Investigator's Rating at 1 week appointment	1.9	1 to 3	0.6

Figure 1: Inflammatory Cascade

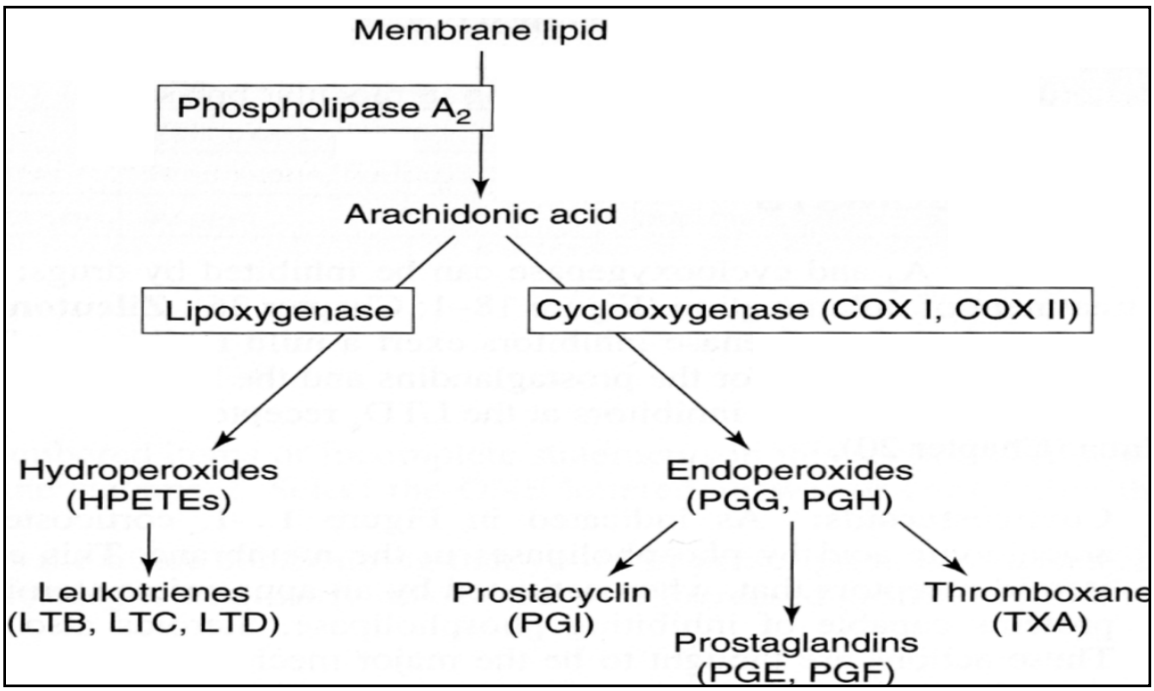


Figure 2: Inflammatory Cascade, NSAIDs and Corticosteroids

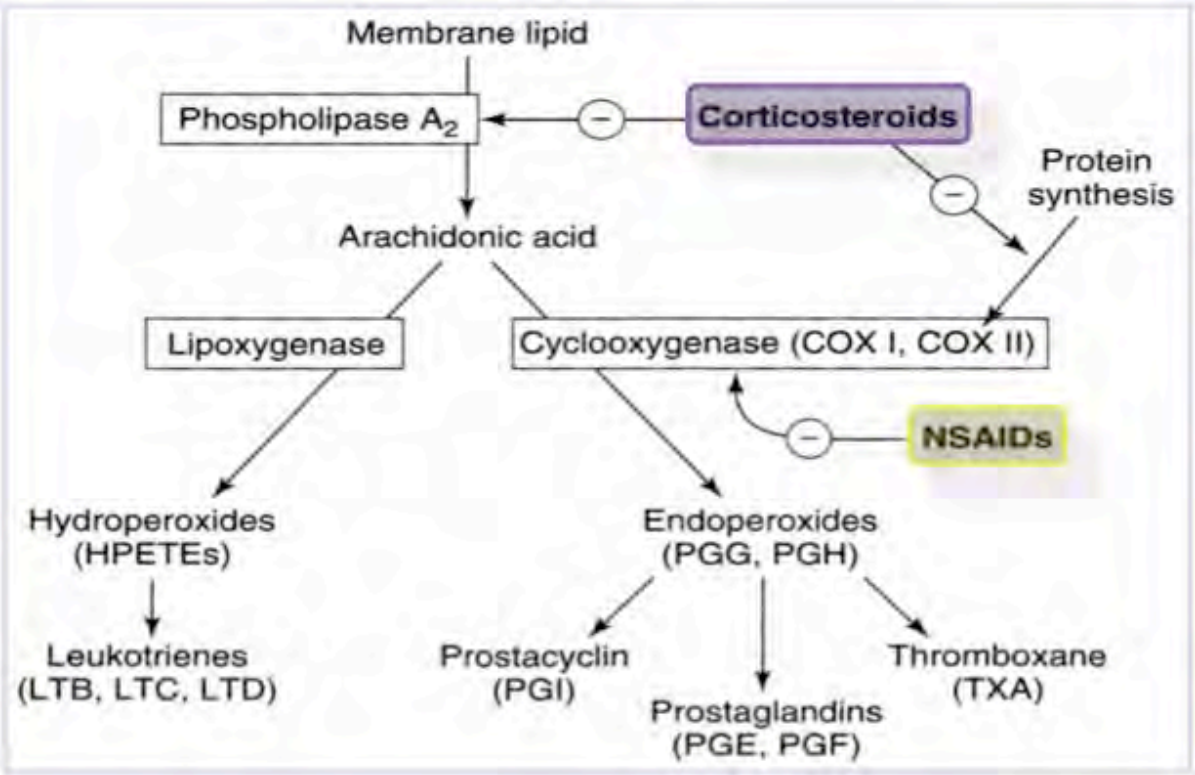
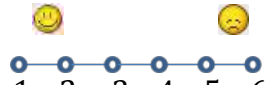
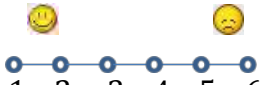
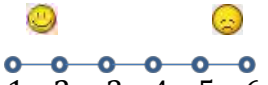
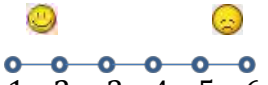
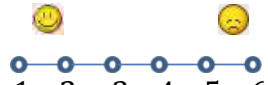
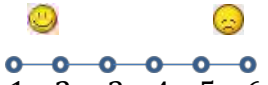
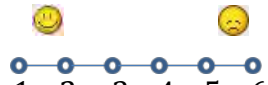
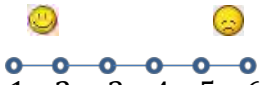
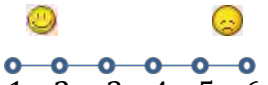
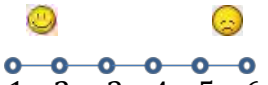
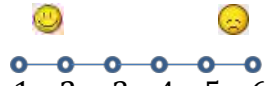
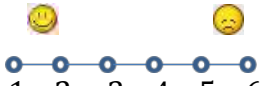
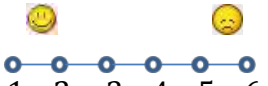
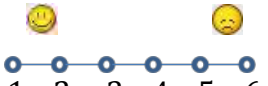


Figure 3: Patient Survey

Date:	Tooth Type:
Investigator: Elena Kan, DDS	Diagnosis:

Dear Participant:
As part of this research study, we require you to complete the chart below regarding your condition. You are asked to examine and rate yourself in 4 categories– A through D (Pain, Swelling, Bruising and Healing) during the 4 days and on the day 7 following your surgery. Each day (days 1-4 and day7), examine yourself and circle the appropriate rating number in each category.

	Categories			
	A. PAIN	B. SWELLING	C. BRUISING (DISCOLORATION)	D. INTRA-ORAL HEALING (WOUND HEALING)
24 hours (1 Day)	 1 2 3 4 5 6 Any Medication? Yes No	 1 2 3 4 5 6	 1 2 3 4 5 6	 1 2 3 4 5 6
48 hours (2 Days)	 1 2 3 4 5 6 Any Medication? Yes No	 1 2 3 4 5 6	 1 2 3 4 5 6	 1 2 3 4 5 6
72 hours (3 Days)	 1 2 3 4 5 6 Any Medication? Yes No	 1 2 3 4 5 6	 1 2 3 4 5 6	 1 2 3 4 5 6
96 hours (4 Days)	 1 2 3 4 5 6	 1 2 3 4 5 6	 1 2 3 4 5 6	 1 2 3 4 5 6
168 hours (1 Week)	 1 2 3 4 5 6	 1 2 3 4 5 6	 1 2 3 4 5 6	 1 2 3 4 5 6
For Office Use and notation Only:	If you experience significant pain you can take prescribed medication for first 3 days following surgery Tylenol 500mg and Vicodin 5/300 Take both tablets together every 6 hours and record it in the chart. Donotexceed more than 4 doses in one 24 hour period			
Investigator (at 1 week appointment)	 1 2 3 4 5 6	 1 2 3 4 5 6	 1 2 3 4 5 6	 1 2 3 4 5 6

If you have any questions, please call **Dr. Elena Kan** at **704-689-4689**.
Thank you for your participation.

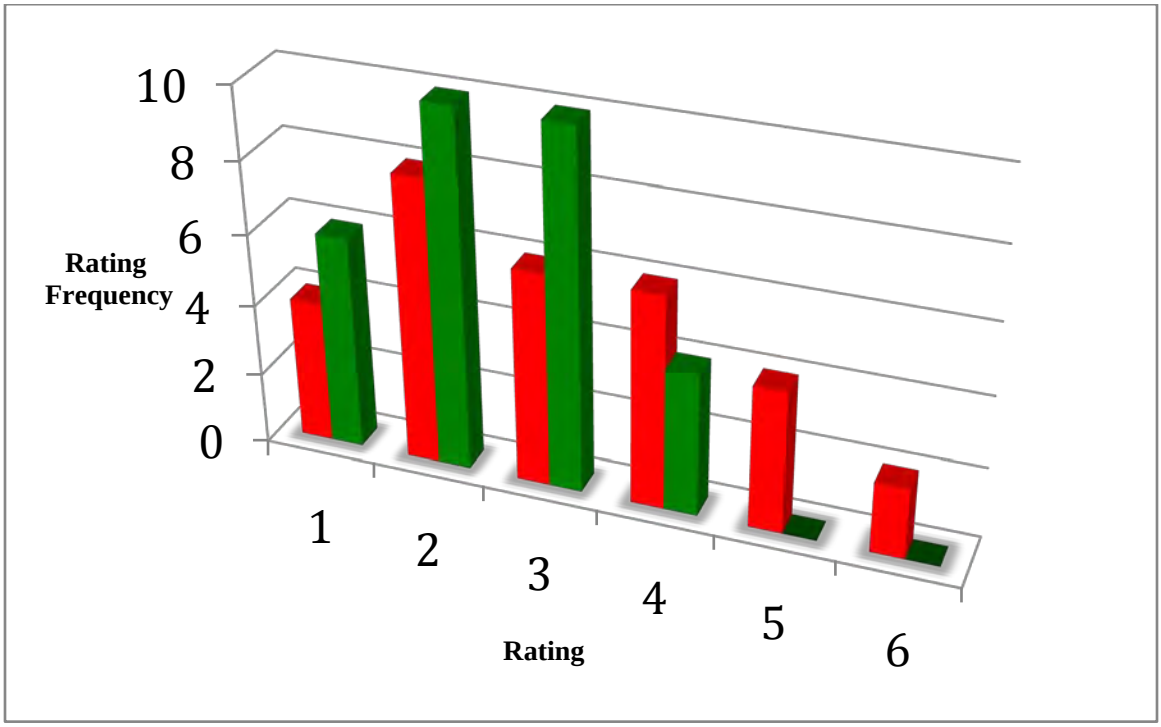
Figure 4: Chi-squared P Values

Values of the Chi-squared distribution

	P										
DF	**0.995**	**0.975**	**0.20**	**0.10**	**0.05**	**0.025**	**0.02**	**0.01**	**0.005**	**0.002**	**0.001**
1	0.0000393	0.000982	1.642	2.706	3.841	5.024	5.412	6.635	7.879	9.550	10.828
2	0.0100	0.0506	3.219	4.605	5.991	7.378	7.824	9.210	10.597	12.429	13.816
3	0.0717	0.216	4.642	6.251	7.815	9.348	9.837	11.345	12.838	14.796	16.266
4	0.207	0.484	5.989	7.779	9.488	11.143	11.668	13.277	14.860	16.924	18.467
5	0.412	0.831	7.289	9.236	11.070	12.833	13.388	15.086	16.750	18.907	20.515
6	0.676	1.237	8.558	10.645	12.592	14.449	15.033	16.812	18.548	20.791	22.458
7	0.989	1.690	9.803	12.017	14.067	16.013	16.622	18.475	20.278	22.601	24.322
8	1.344	2.180	11.030	13.362	15.507	17.535	18.168	20.090	21.955	24.352	26.124
9	1.735	2.700	12.242	14.684	16.919	19.023	19.679	21.666	23.589	26.056	27.877
10	2.156	3.247	13.442	15.987	18.307	20.483	21.161	23.209	25.188	27.722	29.588
11	2.603	3.816	14.631	17.275	19.675	21.920	22.618	24.725	26.757	29.354	31.264
12	3.074	4.404	15.812	18.549	21.026	23.337	24.054	26.217	28.300	30.957	32.909
13	3.565	5.009	16.985	19.812	22.362	24.736	25.472	27.688	29.819	32.535	34.528
14	4.075	5.629	18.151	21.064	23.685	26.119	26.873	29.141	31.319	34.091	36.123
15	4.601	6.262	19.311	22.307	24.996	27.488	28.259	30.578	32.801	35.628	37.697
16	5.142	6.908	20.465	23.542	26.296	28.845	29.633	32.000	34.267	37.146	39.252
17	5.697	7.564	21.615	24.769	27.587	30.191	30.995	33.409	35.718	38.648	40.790
18	6.265	8.231	22.760	25.989	28.869	31.526	32.346	34.805	37.156	40.136	42.312
19	6.844	8.907	23.900	27.204	30.144	32.852	33.687	36.191	38.582	41.610	43.820
20	7.434	9.591	25.038	28.412	31.410	34.170	35.020	37.566	39.997	43.072	45.315
21	8.034	10.283	26.171	29.615	32.671	35.479	36.343	38.932	41.401	44.522	46.797
22	8.643	10.982	27.301	30.813	33.924	36.781	37.659	40.289	42.796	45.962	48.268
23	9.260	11.689	28.429	32.007	35.172	38.076	38.968	41.638	44.181	47.391	49.728
24	9.886	12.401	29.553	33.196	36.415	39.364	40.270	42.980	45.559	48.812	51.179
25	10.520	13.120	30.675	34.382	37.652	40.646	41.566	44.314	46.928	50.223	52.620

Figure 5:

Dexamethasone and Placebo Swelling Rating Frequency Distribution at 24 Hours



Green = dexamethasone **Red = placebo**

Figure 6:

Chi-Square Statistical Analysis Results of Recovery Components Ratings

at 24-hours in 2 x 2 Matrix of High and Low Ratings
(One Degrees of Freedom)