Use of Prophylactic Amoxicillin in Endodontic Microsurgery:

A Pilot Study

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THESIS

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JCN

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADA	American Dental Association
FPS	Four-point scale
g	Grams
IDS	Investigational Drug Service
IRM	Intermediate Restorative Material
mg	Milligrams
mm	Millimeters
MTA	Mineral Trioxide Aggregate
NS-Retx	Non-surgical retreatment
PT	Previously treated
OTC	Over-the-counter
RCT	Root canal therapy
SPSS	Statistical package for the social sciences
S-Retx	Surgical retreatment
tid	Three times a day
UIC COD	University of Illinois at Chicago, College of Dentistry
VAS	Visual analog scale
VRS	Verbal rating scale

SUMMARY

Dentists regularly prescribe systemic antibiotics in patients undergoing surgery. However, the dental literature lacks high level of evidence studies supporting the administration of prophylactic antibiotics in otherwise healthy patients. The purpose of this study is to evaluate the administration of prophylactic antibiotics on the incidence of postoperative pain, infection, and swelling following endodontic microsurgery.

The null hypothesis is that there is no difference in level of postoperative pain, reduction of swelling, or rate of infection when given prophylactic amoxicillin compared to a placebo following endodontic microsurgery.

All subjects were recruited from the patient population in the UIC Endodontics postgraduate clinic from March 1, 2017, to June 16, 2017. Inclusion criteria were patients 18 years and older who are in good general health with no medical contraindications for endodontic microsurgery and have a tooth or teeth with previous root canal treatment that cannot be reasonably managed with non-surgical retreatment. The tooth or teeth receiving treatment must have an adequate coronal restoration and a diagnosis of symptomatic apical periodontitis, asymptomatic apical periodontitis, or chronic apical abscess. Each patient that met the inclusion criteria were randomly given either a placebo or amoxicillin and had their surgical treatment performed by a second year postgraduate resident. Patients were instructed to take ibuprofen 600 mg every 6 hours if necessary for pain management. Patients took two tablets of either 500 mg amoxicillin or placebo 1 hour prior to treatment followed by a 5-day course consisting of amoxicillin 500 mg tid or placebo tid. Postoperative instructions and a visual analogue scale (VAS) for pain were given to the patient at the completion of the surgery.

Pain was recorded preoperatively and postoperatively at 6, 24, 48, and 72 hours, and on the day of suture removal. A 170mm Heft-Parker scale was used, with 0mm representing no pain and 170mm representing maximum possible pain. Patients were also asked to record the use of OTC or prescribed pain medication, including frequency, type, and dosage. Infection was evaluated as either present or absent; the presence of infection was marked by positive purulent drainage from the incision site. Swelling was categorized: no inflammation, intraoral swelling confined to the surgical field being mild inflammation, and moderate inflammation involving extraoral swelling in the region of treatment. Arch, tooth number, demographics, and use of 0.12% Peridex, bone graft, and/or membrane were also recorded. Recall times ranged from 3 to 9 days postoperatively. There was no significant difference ($p > 0.05$) between the control and experimental group in regards to pain/VAS scores or swelling. An infection developed in 1/13 patients, who happened to be in the control group. There was a significant difference found in the total number of ibuprofen taken, with the amoxicillin group being much less. However, the null hypothesis was accepted based on recorded pain intensity using VAS and amount of swelling.

I. INTRODUCTION

A. Background

The primary goal of endodontic treatment is to prevent or eliminate apical periodontitis through effective removal of bacteria, toxins, and protein degradation byproducts from proper cleansing and shaping techniques as well as a three-dimensional hermetic seal of the root canal space (Schilder 1967). Non-surgical and surgical retreatment may be indicated following unsuccessful initial root canal therapy. Endodontic surgery is indicated when there is an adequate root canal filling with persistent symptoms or sinus tract, cases in which nonsurgical retreatment is not possible, or when there is a post greater than 5mm present. Nonsurgical retreatment may not be possible due to separated instruments, calcified canals, ledges, transportation, perforations, or even gross overfills. Further indications for endodontic surgery are presence of irretrievable materials in canals (silver points, pastes, cements, posts), exploratory surgery, repair of resorptive defects or iatrogenic errors, root amputations and hemisection, intentional replantation, or need for a biopsy. Refractory cases that require surgical treatment would include resistant infection or biofilm, cysts, extra-radicular infection, and foreign body reaction (Abramovitz 2002).

Traditional endodontic surgery techniques included no or inadequate magnification and a 45 to 60 degree bevel of the resected root end, which resulted in exposing many dentinal tubules, larger osteotomies, more removal of buccal bone, and commonly missed lingual apices. Materials that were not biocompatible were also frequently used as the root end filling (Kim 2006).

Endodontic microsurgery evolved in the 1990s and combined the use of the dental operating microscope and use of microinstruments; this allowed for more precise and

predictable surgical treatment (Kim 2006). Modern endodontic surgery techniques exposed fewer dentinal tubules due to a 1 to 10 degree bevel and allowed for a uniform 3mm root-end preparation and fill (Gilheany 1994). Microsurgery success rates increased from 59% using traditional techniques to 94% using modern techniques (Setzer 2010).

The use of antibiotics in surgical endodontics has received mixed reviews (Lindeboom 2005) and there has been recent concern about the over-prescribing and overuse of antibiotics, which may lead to increased bacterial resistance. Dentists are the third most common health care provider prescribing antibiotics with 24.5 million prescriptions written in 2013 (CDC 2013). In a survey sent to American Association of Endodontists (AAE) members in 2000, 37% of endodontists routinely prescribed antibiotics for microsurgery (Yingling 2002) despite the recommended use of systemic antibiotics being limited to patients with systemic signs of infection such as cellulitis, lymphadenopathy, swelling, and fever (Cope 2014). Of the respondents in the AAE survey, an average of 9.25 antibiotic prescriptions were written per week for varying treatment procedures, some solely on the basis of patient demand, expectations of the referring dentist, or presumed medical-legal reasons. Endodontic surgery is typically performed in cases with a localized area of pathosis and overall healthy tissue. In non-immunocompromised patients and with sterile surgical technique, antibiotics are not indicated (Yingling 2002). Furthermore, the endodontic literature lacks high level of evidence studies supporting the administration of antibiotics in otherwise healthy and stable patients.

B. Significance of the study

The significance of this study is the potential to help reduce the inappropriate use of antibiotics and possibly decrease the risk of antibiotic resistance. The main goal is to provide preliminary support and justification for a larger scale study on the topic. If positive results are found for the use of prophylactic antibiotics, this could justify the use in endodontic microsurgery. Based on findings from this pilot study, the protocol may be modified and appropriate sample size calculation should be possible.

C. Specific Aims

The purpose of this clinical study is to assess the use of prophylactic antibiotics on post-operative pain, infection, and swelling following endodontic microsurgery. The objectives are three-fold:

- Obtain and evaluate pain levels following endodontic microsurgery using a Heft-Parker VAS.
- Evaluate the presence of infection and swelling to determine the success of soft tissue healing.
- Assess whether there is an association between prophylactic antibiotics and postoperative pain, swelling, and infection.

D. Hypothesis

The following null hypothesis was tested: There is no significant difference in postoperative pain, swelling, or infection following endodontic microsurgery when given prophylactic amoxicillin compared to a placebo.

II. REVIEW OF THE LITERATURE

A. Postoperative Pain and Swelling In Endodontic Surgery

Penarrocha showed no significant difference between pre- and postoperative pain following periapical surgery at 7 days postoperatively. Swelling and pain reached its peak at 2 days postoperatively, however the most pain was observed within the first 48 hours after surgery. Mandibular anterior teeth were found to be associated with the most discomfort whereas maxillary molars and mandibular premolars had the least. Smaller osteotomies less than 1 centimeter were associated with less pain than osteotomies greater than 1 centimeter, however size had no correlation with inflammation (Penarrocha 2006). In a study comparing root-end resection using either Mineral Trioxide Aggregate (MTA) or Intermediate Restorative Material (IRM), Chong and Pitt Ford found that within the first 6 hours following endodontic surgery, 90% of patients experienced some level of pain with 37% of patients choosing not to take any form of analgesics. Along with a decline in VAS measurements, there was also a continuous decline in postoperative pain with 82% and 72% of patients reporting discomfort after 24 hours and 48 hours respectively. These findings, however, were not statistically significant (Chong 2005).

In a study by Christiansen et al evaluating pain levels following periapical microsurgery in 42 patients with apical periodontitis, there was a significant difference in postoperative discomfort with VAS scores peaking at 3 hours postoperatively. Swelling was at its highest 1 day postoperatively and there was no significant difference in swelling when comparing 1, 2, and 3 days postoperatively. Interestingly, the author found a significantly higher VAS score for pain and swelling among women compared to men 3 hours postoperatively for pain and 1 day

postoperatively for swelling. Overall, it was found that there was little discomfort and only moderate swelling following endodontic surgery (Christiansen 2008).

B. Prophylactic Antibiotics in Endodontics

The use of prophylactic antibiotics in surgical endodontics is controversial (Lindeboom 2005) and there is a growing concern about the over-prescribing and overuse of antibiotics, which may lead to increased frequency of bacterial resistance. The inappropriate use of antibiotics creates a higher risk for possible anaphylactic reactions while exposing the patient to unnecessary side effects (Cope 2014) such as risk of hospital infection (Lindeboom 2003). It also inadvertently creates an increased expectation and dependence among people for antibiotics (Cope 2014) thus, it is essential that antibiotics be prescribed only when there are expected clinical benefits. Dentists are the third most common health care provider prescribing antibiotics, with 24.5 million prescriptions written in 2013 (CDC 2013). In a survey sent to American Association of Endodontists members in 2000, 37% of endodontists routinely prescribed antibiotics for microsurgery (Yingling 2002) despite the recommendation that use of antibiotics should be limited to patients with systemic signs of infection such as cellulitis, lymphadenopathy, swelling, and fever (Cope 2014). Of the respondents in the AAE survey, an average of 9.25 antibiotic prescriptions were written per week for varying treatment procedures, some solely on the basis of patient demand, expectations of the referring dentist, or presumed medical-legal reasons. Endodontic surgery is typically performed in situations with a localized area of pathosis and overall healthy tissue. In non-immunocompromised patients and with sterile surgical technique, antibiotics are generally not indicated (Yingling 2002).

The primary etiology of persistent apical periodontitis is microorganisms; the rationale for prescribing pre-operative and/or post-operative antibiotics is that surgical intervention could cause a bacterial infection within the surgical site (Lindeboom 2005). There is much controversy on this issue. The use of systemic antibiotics has not been proven to help reduce pain or swelling in cases of apical periodontitis with the absence of systemic involvement (Cope 2014). Several studies have shown no significant difference in pain levels between the control and experimental groups. The effective dosage of prophylactic clindamycin for the prevention of postoperative infections following endodontic microsurgery was assessed in a double-blind placebo-controlled trial. Randomly selected patients received 600 mg of clindamycin preoperatively. After a 28-month evaluation with a 100% recall rate, 2 infections had developed in the experimental group and 4 wound infections had developed in the control group, all occurring within the first 2 weeks and presenting as subcutaneous fluctuant swelling. However, there was no statistically significant difference found in regards to the use of prophylactic antibiotics in preventing postoperative infections (Lindeboom 2005).

There is a lack of double-blind, randomized controlled trials supporting or opposing the use of systemic antibiotics for endodontic surgery (Lindeboom 2005). A Cochrane Database Review searched for randomized controlled trials using systemic antibiotics in patients with symptomatic apical periodontitis or acute apical abscess that were treated with either extraction, incision and drainage, or endodontic therapy with or without antibiotics and found two articles that met the specified criteria. Both studies found no statistically significant difference in pain or swelling between the experimental group receiving oral antibiotics compared to the control group receiving the placebo with initial root canal therapy. This review showed that there is

insufficient data determining the effects of antibiotics when used for apical periodontitis and that the evidence that is currently available is of low quality (Cope 2014).

C. Prophylactic Antibiotics in Dental Surgical Procedures

Escalante evaluated the effects of a single dose of 500 mg azithromycin or 2 g amoxicillin prior to one-stage implant placement and discovered patients taking azithromycin had fewer proinflammatory cytokines and chemokines in both the gingival crevicular fluid from adjacent teeth and the peri-implant crevicular fluid (Escalante 2015). A separate study found that antibiotic prophylaxis had a significant effect in reducing the risk for infection complications in intra-oral bone grafts. Either 2 grams pheneticillin or a placebo was given to 20 patients 1 hour prior to the procedure. Of the 20 patients, 2 developed wound infections at the receptor site, 2 at both the receptor and donor site, and 1 at the donor site within the first 10 days postoperatively. All 5 patients were in the placebo group and all cultures had penicillin-sensitive streptococci present (Lindeboom 2003).

In a study comparing the duration of antibiotics in orthognathic surgeries there was a significantly higher occurrence of postoperative infections when given 1 day of antibiotics versus 5 days (6.3 times greater incidence of infection in the 1-day group). It was concluded that antibiotic prophylaxis administration should continue for longer than just the immediate postoperative period in order to provide adequate coverage (Bentley 1999). A Cochrane Database Systematic Review that evaluated the effects of antibiotic prophylaxis in patients undergoing orthognathic surgery pooled 7 trials that administered either a single preoperative dose, a short-term dosage that consisted of antibiotic administration before or during surgery and/or the same day of surgery, and a long-term dosage that consisted of antibiotics before or

during surgery and longer than 1 day postoperatively. The search found a 26% to 76% reduction in occurrence of infections with the long-term antibiotic prophylaxis group. It was concluded that administration or prophylactic antibiotics for more than 1 day postoperatively decreased the risk of surgical site infections in patients undergoing orthognathic surgery compared to a single dose or a short-term dose (Brignardello-Peterson 2015). In another study involving the management of postoperative endodontic pain with either ibuprofen only or ibuprofen and amoxicillin/clavulanic acid, there was a significant reduction in pain and consumption of NSAIDs in the antibiotic group (Alsomadi 2015). The number of adverse reactions to amoxicillin compared to clindamycin was found to be significantly lower in a study evaluating the incidence of reactions when given prophylactically for infective endocarditis in an English population. Data was recorded for prescriptions of either a single oral dose of 2 g amoxicillin or 600 mg clindamycin. For 3 million prescriptions written for amoxicillin, there were zero fatal reactions reported. Furthermore, amoxicillin was associated with 23 non-fatal reactions per million prescriptions written. Clindamycin, on the other hand, was found to have 13 fatal and 149 non-fatal adverse reactions per million prescriptions with most being *Clostridium difficile* infections (Thornhill 2015). A similar finding demonstrated a 3% overall risk of adverse reactions associated with amoxicillin (Farbod 2009).

D. Use of Visual Analogue Scales In Measuring Dental Pain

Visual analogue scales were originally utilized for subjective measurements in psychology and education. When designing a visual analogue scale, several ideal criteria should be met: the observed response should be defined, extremes of the sensation should be decided, descriptive terms should be easily understood and short, median of the sensations should be

located in the center, no superimposition of numbers so as not to interfere with the distribution of results, and the length of the line should be measured as a unit (Seymour 1985). In a study by Seymour, two VAS were compared with a numerical scale and a verbal descriptive scale to determine the severity of postoperative pain in patients undergoing extraction of impacted mandibular third molars. Patients were asked to record their level of pain at ten different time intervals, with each interval being on a separate sheet of paper and each sheet being removed as soon as it had been completed so that patients were not able to reference previous recordings. This study found a high correlation between the two VAS and numerical scale and were more sensitive in determining differences in pain intensity. Two VAS were given to evaluate reliability and validity, with a high correlation found between the two. It was concluded that a visual analogue scale is a reliable technique for recording dental pain (Seymour 1982). Another study compared using a VAS and a 4-point scale (FPS) in patients with chronic inflammatory or degenerative arthropathy. Patients were given either paracetamol or dihydrocodeine therapy and were asked to record their level of pain. This study also found the VAS to be more accurate and sensitive in defining pain intensity (Joyce 1975). When comparing a verbal rating scale (VRS) with a visual analogue scale in patients with severe pain due to malignant disease, the VAS provided a more accurate depiction of pain levels experienced. Patients were given in random order a furanone derivative, pentazocine, and placebo on three separate days. Pain intensity was recorded using the VRS and VAS at four time intervals. Because this study had an inadequate sample size (n=6), there was no significant difference found amongst any of the groups. However, the VRS had a higher F-ratio, indicating that it artificially amplified the effect of drugs given (Ohnhaus 1975).

III. MATERIALS AND METHODS

A. Study Design

The protocol and informed consent forms were approved by the University of Illinois at Chicago Institutional Review Board (protocol #2016-1178). Patients referred for endodontic treatment at the University of Illinois-Chicago College of Dentistry (UIC COD) Postgraduate Endodontics Clinic underwent a radiographic and clinical evaluation for diagnostic and treatment purposes. Teeth diagnosed with symptomatic apical periodontitis, asymptomatic apical periodontitis, or chronic apical abscess, adequate root canal filling (pulpal diagnosis of previously treated), adequate coronal restoration without signs of marginal leakage or structural breakdown, and in which non-surgical retreatment would not provide significant improvement were treatment planned for surgical retreatment. Patients selected for participation were 18 years and older, healthy, and without any debilitating or uncontrolled systemic diseases. Non-surgical retreatment root canal therapy is deemed impractical or unlikely to improve on previous treatment for various reasons such as iatrogenic error (separated instruments, ledges, perforations, strips/zips, overfills), irretrievable material in canals (post/core, silver points, pastes, and cements), or resorptive defects. Teeth that could be predictably managed with non-surgical retreatment and patients allergic to amoxicillin or currently taking antibiotics were excluded from the study. Other exclusion criteria were non-English speaking patients, severe periodontitis, acute symptoms of infection such as swelling and fever, anyone required to take premedication, pregnancy, and patients with phenylketonuria or currently taking methotrexate, and patients in which prophylactic antibiotics is indicated for a systemic disease or medical condition as stated by the current ADA guidelines such as patients with prosthetic cardiac valve or prosthetic material used for

cardiac valve repair, history of infective endocarditis, cardiac transplant that develops cardiac valvulopathy, and congenital heart disease including unrepaired cyanotic congenital heart disease (palliative shunts, conduits), completely repaired congenital heart defect with prosthetic material or device during the first six months after the procedure, and any repaired congenital heart defect with residual defect at the site or adjacent to the site of a prosthetic patch or a prosthetic device. Each patient was evaluated for participation using a checklist found in Appendix A. All participants were provided with written information and consent about the study. There was no financial incentive and patients were informed that they could withdraw from the study at any time. Subjects had their treatment performed by four of the second year postgraduate endodontic residents under direct faculty supervision. The usual surgical treatment protocol was not modified in any way except for the study intervention (placebo or active drug). All surgical procedures followed current microsurgical techniques and standards. Patients were instructed to take ibuprofen 600 mg every 6 hours as needed for postoperative pain. Patients were also given Norco^{TM} as a rescue medication. This pain management strategy is standard operating procedure in our clinic. The placebo was prepared by the UIC Investigational Drug Service (IDS) and the amoxicillin was encapsulated so that both drugs appeared identical. The drug bottles were labeled with identification numbers. Patients were randomized into two groups by following the identification numbers in sequential order so that provider, investigator, and patient were blinded. Subjects took two tablets of either 500 mg amoxicillin or placebo 1 hour prior to treatment followed by a 5-day course consisting of amoxicillin 500 mg tid or placebo tid.

B. Data Collection

Postoperative instructions and a Heft Parker VAS shown in Appendix B were given to record pain intensity at six time intervals. The VAS was on a 170mm horizontal scale and patients were instructed to use the verbal descriptors as a guide with the left most boundary being no pain and the right being maximum possible pain. Pain was recorded preoperatively and at 6, 24, 48, and 72 hours, as well as on the day of suture removal by placing a vertical mark on a horizontal VAS. Patients were also asked to record any consumption of over-the-counter or prescribed pain relievers, how often, the type, and dosage (Appendix C). The analgesic log and VAS were collected on the day of suture removal. Infection was evaluated as either present or absent at the date of suture removal; the presence of infection was marked by positive purulent drainage from the incision, induration, and/or fever. Swelling was evaluated during the suture removal visit as well and was categorized as no inflammation, mild inflammation, or moderate inflammation. Mild inflammation pertained to intraoral swelling confined to the surgical field whereas moderate inflammation involved extraoral swelling in the region of where treatment was performed. Arch, tooth number, demographics, and use of 0.12% Peridex, bone graft, and/or membrane were also recorded.

IV. STATISTICAL ANALYSIS

The data were analyzed using ANOVA and t-test with a statistics software program (SPSS for Windows Version 22, SPSS Inc.). Significance value was set at $p < 0.05$ for all statistical tests. Since this is a pilot study, a formal sample size calculation was not performed. Data analysis from this study will form the basis for sample size calculation for a subsequent expanded version of this study.

V. RESULTS

There were a total of 28 surgeries performed in the UIC Endodontics department between the time of March 1, 2017, through June 16, 2017. Of those 28 surgeries, 14 were excluded. Reasons for exclusion are shown in Table 1.

TABLE 1: EXCLUDED PATIENTS

Reason for Exclusion	Number of Patients
Currently Taking Antibiotics	2
Non-English Speaking	4
< 18 years old	1
Premedication Required	1
Allergic to Penicillin/Amoxicillin	1
Inadequate Coronal Restoration	1
Not Interested in Participating	4

The included participants ranged from age 18 to 77 years old with an average age of 47 years. There were 6 males and 7 females. A majority of the subjects (9/13) presented with no preoperative pain. There was an almost even distribution of mandibular (5/13) and maxillary (8/13) teeth being treated. 10/13 patients were prescribed 0.12% Peridex postoperatively. Only 4/13 patients received a bone graft and membrane. The average day until suture removal was 5.9

days with it ranging from 3 to 9 days. One of the 14 included patients did not return for suture removal, and one did not properly record analgesics taken; both subjects were in the control group. The average number of days patients used NSAIDs for pain relief was 2.8 days and ranged from 0 to 10 days. The use of the rescue medication acetaminophen/hydrocodone (Norco™) was not analyzed because there was a minimal amount taken by all patients in both experimental and control groups. Within the first four days postoperatively, one patient in the amoxicillin group consumed 10 tablets of Norco™ 5/325 and two patients in the placebo group consumed 7 and 8 tablets respectively. Patients were instructed to take ibuprofen for the discomfort and to supplement with Norco™ if needed. All three patients who consumed the rescue medication used it solely without taking the ibuprofen as directed. The total number of NSAIDs taken in the placebo group was 44 tablets and 23 tablets for the experimental group. The total number of ibuprofen taken for each day is indicated in Table 2. The average VAS scores for each group is shown in Table 3 with the peak intensity of pain for all patients occurring around 24 hours.

TABLE II: TOTAL NUMBER OF NSAID CONSUMPTION

Day	Amoxicillin	Placebo
1	4	6
2	7	13
3	6	13
4	4	8
5+	2	4

TABLE III: AVERAGE VAS SCORES (mm)

	Amoxicillin (n= 6)	SD	Placebo (n= 7)	SD
Preoperative	10.7	±5.18	6.3	±14.44
6 hours postoperative	45.3	±22.98	31.9	±27.67
24 hours postoperative	48.5	±17.71	33.1	±20.67
48 hours postoperative	33.3	±26.53	24.6	±32.67
72 hours postoperative	29.3	±26.69	24.3	±25.78
Day of Suture Removal	22.3	±24.45	22.4	±21.44

When comparing VAS scores for the placebo and amoxicillin groups at each time interval, there was no significant difference in pain relief ($p= 0.109$, $p>0.05$). There was a difference ($p=0.010$, $p<0.05$) in the total number of NSAIDs taken with the amoxicillin group being significantly less likely to take NSAIDs. One patient developed an infection in the placebo group. There was no significant difference found in regards to swelling between either group ($p=0.887$, $p > 0.05$).

VI. DISCUSSION

The aim of this study was to determine whether there was a benefit in prescribing prophylactic antibiotics for surgical endodontic patients in regards to postoperative pain, swelling, and infection. This study was double-blinded, placebo-controlled, randomized, and prospective in nature.

Widespread use of antibiotics has caused an increase in the prevalence of resistant microorganisms. Bacteria can develop resistance immediately after introduction of a new drug. Furthermore, almost every oral microorganism has been found to have some degree of resistance to antibacterial medicaments. This resistance is due to both spontaneous genetic mutations and more so to the overuse of antibiotics (ADA Council 2004). Bacterial resistance is either intrinsic or acquired, with some species having more natural resistance to antibiotics than others. Acquired resistance is due to genetic mutations or horizontal transfer of resistant genes. Intrinsic resistance requires no genetic alteration; an example is mycoplasma in which it is resistant to beta lactams because it lacks peptidoglycan. Antibiotic resistance occurs as a result of decreased uptake, increased export, inactivation or alteration of the drug target, a new drug resistant target, hydrolysis of the drug, or modification of the antibiotic (Normark 2002).

Bacterial resistance exemplifies Darwinian selection (Normark 2002), therefore appropriate use of antibiotics can prolong their efficacy. A systematic review and meta-analysis demonstrated a decrease in oral infections with the use of prophylatic antibiotics only with extractions. There was no significant difference between the antibiotic and placebo in regards to implant and endodontic surgery (Moreno-Drada 2016). The drug and dosage used in this study was partly determined by a study evaluating the incidence and nature of adverse reactions to either amoxicillin or clindamycin prescribed to patients in England given prophylactic antibiotics

for prevention of endocarditis. The study found that there were minimal adverse reactions to amoxicillin whereas clindamycin was associated with both fatal and non-fatal reactions, *Clostridium difficile* infections being the most common (Thornhill 2015). The usual dosage of amoxicillin for dental infections is 500mg tid for 5 to 7 days (Baumgartner 2006).

Only one endodontic article was found in regards to prophylactic antibiotics for endodontic surgeries. The methodology used in this study was similar to our study except that 600mg of clindamycin was used rather than 500mg amoxicillin. Randomly selected patients received 600 mg of clindamycin preoperatively. After a 28-month evaluation, 2 infections had developed in the experimental group and 4 infections had developed in the control group. A total of 256 patients underwent endodontic surgery with an overall infection rate of 2.3%. There was no statistically significant difference found in regards to the use of prophylactic antibiotics in preventing postoperative infections (Lindeboom 2005). To ensure a high recall rate and assess outcomes in a more tangible manner, our study utilized an average 5 to 7 day recall so that data could be collected on the day of suture removal.

Penarrocha showed no significant difference in pain following periapical surgery with the most pain being observed within the first 48 hours after surgery (2006). Our study had similar findings in which there was no significant difference ($p < 0.05$) in VAS scores between the control and experimental group. However, peak pain intensity developed around 24 hours and did not begin to decrease until after 48 hours postoperatively. A similar finding was found in another study in which 82% of patients at 24 hours postoperatively and 72% of patients at 48 hours postoperatively experienced pain following endodontic surgery (Chong 2005). Similarly, Alsomadi found a significant reduction in pain and consumption of NSAIDs in the antibiotic group (2015). Although our study had no significant difference in VAS scores between groups,

there was a significant difference in the total amount of NSAIDs taken ($p < 0.05$). Our null hypothesis was that prophylactic amoxicillin would have no significant effect on pain relief, swelling, or infection over a placebo. Since $p= 0.109$ for VAS over all 6 time intervals, we accept the null hypothesis and conclude that there is no difference. Although amoxicillin had no significant effect on pain relief as a whole, using an independent samples t-test at 24 hours postoperatively showed a significant effect on pain with $p= 0.040$. This may imply that amoxicillin may provide some pain relief following endodontic microsurgery for at least the first 24 hours following treatment.

VII. CLINICAL RELEVANCE AND LIMITATIONS

There is no standard regimen for prophylactic antibiotics following endodontic microsurgery. Microorgansims are the primary cause of apical periodontitis. The rationale for prescribing antibiotics is that surgical intervention can superimpose the bacterial infection in the surgical field (Lindeboom 2005). Although the research subjects may not have benefited directly from this research, the knowledge gained will help inform future best practice guidelines. Dental pain can have a negative effect on quality of life. One of the primary objectives for dental practitioners is to implement strategies for controlling pain and infection. Therefore, if antibiotics are found to decrease post-operative swelling, pain, and infection the overall success of treatment may be improved as well as having a positive effect on patients' comfort.

One of the biggest limitations of this study was sample size. The goal of this initial pilot study was to include 30 patients, but only slightly less than half of that number were actually enrolled. Data collection was also heavily dependent upon patient compliance. One subject from the placebo group was excluded during the study for not returning for follow-up. Another patient did not properly record analgesics taken, however the VAS was included in this analysis. With the patients who did record analgesics and pain intensity, we are assuming that they understood and correctly filled out the data. There is a possibility that the use of analgesics masked the pain intensity. Some of the subjects were prescribed a 0.12% Peridex rinse, which could also affect the tissue healing. Furthermore, there was no restriction to tooth type. All treatment was performed using modern surgical techniques, however there was no standardization of surgical design or procedure. Another factor determining postoperative healing is clinical experience. Our total time for surgical treatment and size of

osteotomies are likely to be prolonged and larger compared to a more experienced clinician. Increased surgical time and larger osteotomies greater than 1 centimeter have been associated with more pain (Penarrocha 2006). Whether there was a fenestration of the bone due to the lesion was not recorded. This could be a factor affecting both time of treatment and size of osteotomy. This study evaluated presence of swelling at the day of suture removal when swelling typically peaks after 24 to 48 hours postoperatively (Christiansen 2008). Therefore, the evaluation within this study is slightly skewed since the patient does not return for a clinical exam until several days after treatment.

VIII. FUTURE RESEARCH

Findings from this study show that future research with a larger sample size is needed. This will allow us to have a more accurate evaluation on whether there is a difference with postoperative healing and pain using prophylactic antibiotics. This study also found a significant difference in amount of NSAIDs taken with the amoxicillin group. A larger sample size will be able to provide a more reliable depiction of whether there is a true correlation or not. Adding a Spanish language consent may be a potential method for controlling excluded patients as well as possibly providing a financial incentive.

IX. CONCLUSION

In conclusion, within the parameters of this study, the results demonstrated that there is no significant difference in postoperative pain based on VAS measurements, level of swelling, and rate of infection when given prophylactic amoxicillin compared to a placebo. The experimental group took significantly fewer NSAID doses than the control group.

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APPENDICES

APPENDIX A

Eligibility Checklist

Use of Prophylactic Amoxicillin in Endodontic Microsurgery: A Pilot Study

Principal Investigator:
Julia Nguyen, DDS, julngu@uic.edu

Study Location: Postgraduate Endodontics Clinic, Room 313, College of Dentistry, University of Illinois at Chicago

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- ☐ 18 years or older
- ☐ Understands English
- ☐ No contraindications to endodontic surgery
- ☐ No indication for antibiotic premedication
- ☐ Not allergic to penicillin or amoxicillin
- ☐ Not currently taking antibiotics or methotrexate
- ☐ Does not have phenylketonuria, kidney disease, or currently on dialysis in which amoxicillin would be contraindicated
- ☐ Tooth with pulpal diagnosis of previously treated
- ☐ Tooth with periapical periodontitis or chronic apical abscess
- ☐ Adequate coronal restoration
- ☐ Non-surgical retreatment is impractical or unlikely to improve on previous treatment
- ☐ Does not have severe periodontitis
- ☐ If female, not pregnant
- ☐ No acute symptoms of infection

APPENDIX B

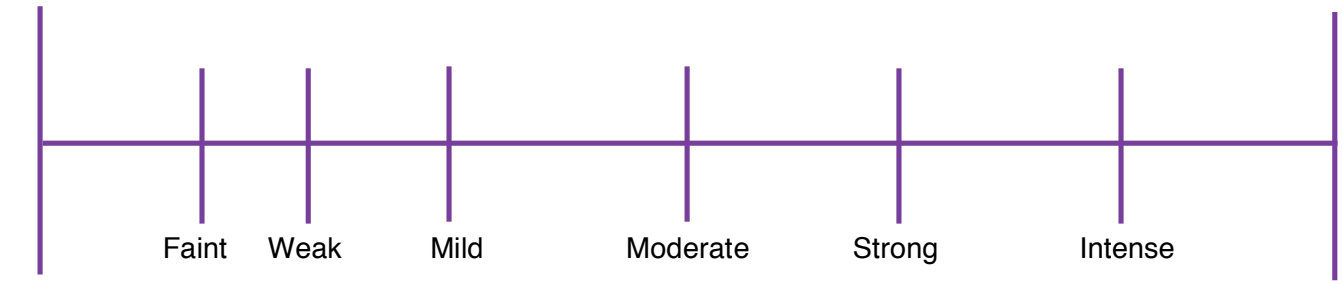
Pain Log

Identification # _____

Directions: Please record your current pain level by placing a single hashmark at each given time frame.

Preoperative:

Time recorded: _____am/pm

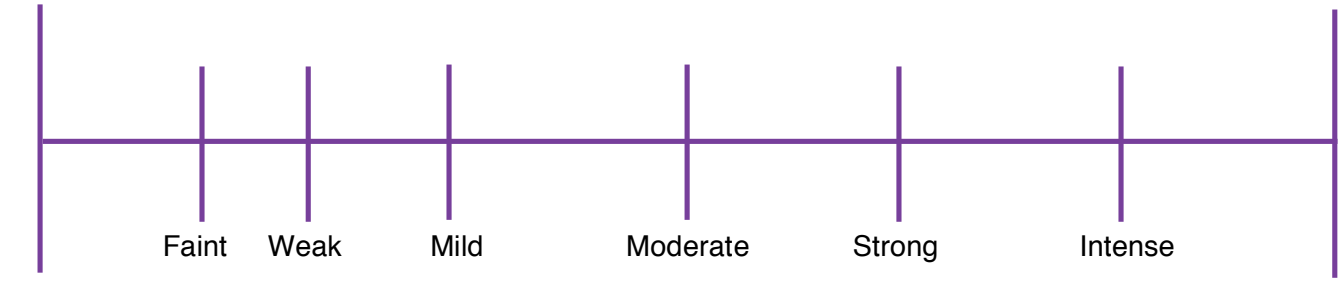


None

Maximum Possible

6 hours postoperative:

Time: _____am/pm
Actual time recorded: _____am/pm



None

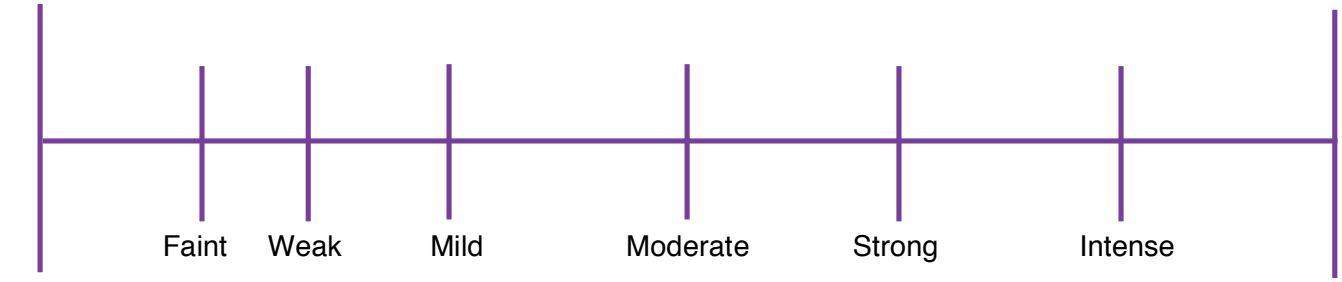
Maximum Possible

APPENDIX B (CONTINUED)

Identification # _____

24 hours postoperative:

Time: _____am/pm
Actual time recorded: _____am/pm

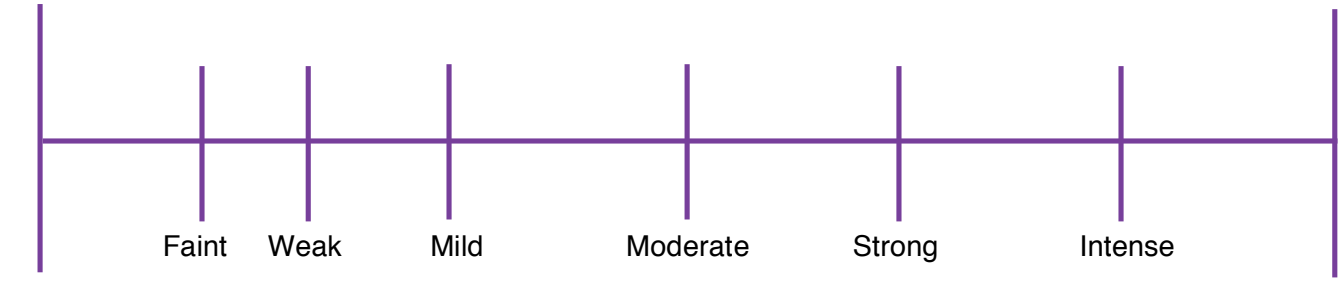


None

Maximum Possible

48 hours postoperative:

Time: _____am/pm
Actual time recorded: _____am/pm



None

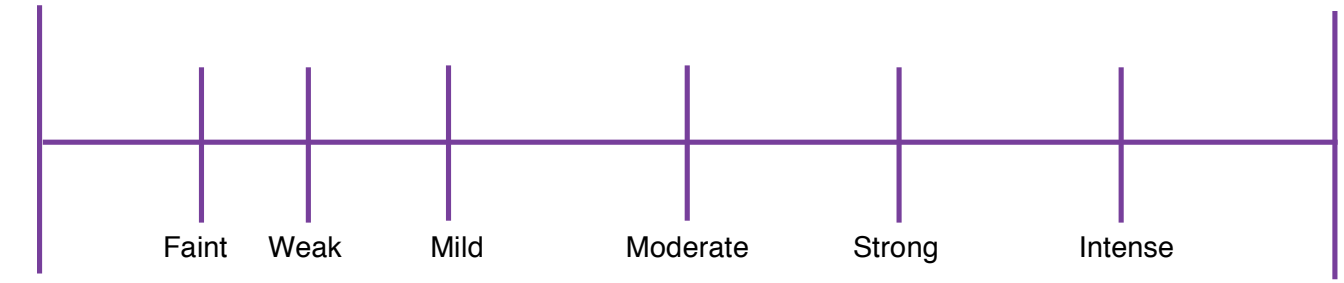
Maximum Possible

APPENDIX B (CONTINUED)

Identification # _____

72 hours postoperative:

Time: _____am/pm
Actual time recorded: _____am/pm

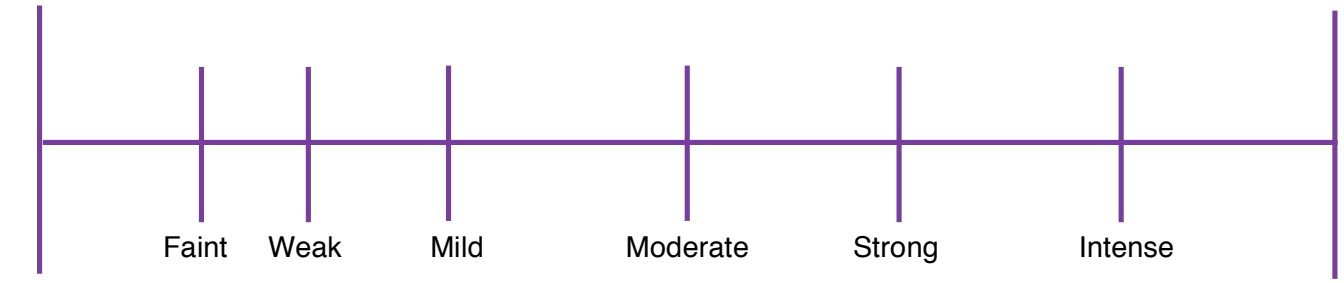


None

Maximum Possible

Day of suture removal:

Date: ___/___/___
Actual time recorded: _____am/pm



None

Maximum Possible

APPENDIX C

Pain Medication Log

Identification # _____

Directions: Please record the following information if any pain relievers are taken following your surgery.

Name of Medication	Time Taken	Dosage	Number of tablets

APPENDIX D

Raw Data for VAS Scores

Sequence #	VAS pre-op (mm)	VAS 6 hr (mm)	VAS 24 hr (mm)	VAS 48 hr (mm)	VAS 72 hr (mm)	VAS suture (mm)	Placebo/ Amoxicillin
1	11	5	3	5	2	3	P
2	0	55	75	55	53	21	A
3	3	26	41	57	25	25	A
4	0	0	0	0	0	0	P
5	4	66	10	2	0	2	P
6	2	6	35	1	14	3	A
7	9	20	29	34	34	21	P
8	0	21	22	1	1	1	A
9	54	53	34	0	0	0	A
10	N/A	N/A	N/A	N/A	N/A	N/A	P
11	1	51	52	108	108	108	P
12	5	111	84	86	83	84	A
13	2	22	1	1	2	3	P
14	17	59	38	22	24	20	P

APPENDIX E

Protocol Approval Letter

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Initial Review (Response To Modifications)

February 28, 2017

Julia Nguyen
Endodontics
801 S. Paulina
Room 313, M/C 642
Chicago, IL 60612
Phone: (479) 799-2928

RE: Protocol # 2016-1178
"Use of Prophylactic Amoxicillin in Endodontic Microsurgery: A Pilot Study"

Dear Dr. Nguyen:

Your Initial Review (Response To Modifications) was reviewed and approved by the Expedited review process on February 24, 2017. You may now begin your research

Please note the following information about your approved research protocol:

Protocol Approval Period:	February 24, 2017 - February 24, 2018
Approved Subject Enrollment #:	30
Additional Determinations for Research Involving Minors:	These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites:	UIC
Sponsor:	Department of Endodontics
PAF#:	Not available
Grant/Contract No:	Not available
Grant/Contract Title:	Not available
Research Protocol(s):	

APPENDIX E (CONTINUED)

a) Use of Prophylactic Amoxicillin In Endodontic Microsurgery, A Pilot Study, Version 3, February 16, 2017

Recruitment Material(s):

a) None

Informed Consent(s):

a) Amoxicillin for Endodontic Microsurgery, version 3, 2.16.2017

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
11/23/2016	Initial Review	Convened	12/07/2016	Deferred
01/18/2017	Response To Deferred	Convened	02/01/2017	Modifications Required
02/17/2017	Response To Modifications	Expedited	02/24/2017	Approved

Please remember to:

→ Use your **research protocol number** (2016-1178) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-1835. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Jonathan W. Leigh, MPH, CIP
IRB Coordinator, IRB # 1
Office for the Protection of Research Subjects

APPENDIX E (CONTINUED)

Enclosure(s):
Note The approved study materials listed below will be sent as an attachment with a separate email.

1. **UIC Investigator Responsibilities, Protection of Human Research Subjects**
2. **Informed Consent Document(s):**
   a) Amoxicillin for Endodontic Microsurgery, version 3, 2.16.2017

cc: Lyndon Cooper, Dentistry, Associate Dean for Research, M/C 642
Bradford R. Johnson, Faculty Sponsor, M/C 642
IDS, Pharmacy Practice, M/C 883

APPENDIX F:

Use of Prophylactic Amoxicillin In Endodontic Microsurgery: A Pilot Study

Principal Investigator:

Julia Nguyen[1], DDS, julngu@uic.edu

Faculty Sponsor:

Bradford Johnson[1], DDS, MHPE

[1]Endodontics Department, University of Illinois at Chicago

Faculty Sponsor:

Bradford Johnson[1], DDS, MHPE

[1]Endodontics Department, University of Illinois at Chicago

Study Location(s): Postgraduate Endodontics Clinic, Room 313, College of Dentistry, University of Illinois at Chicago

Version: 3

Date: February 16, 2017

TABLE OF CONTENTS

Page

LIST OF ABBREVIATIONS

ADA	American Dental Association
EHR	Electronic health record
g	Grams
mg	Milligrams
mm	Millimeters
NS-Retx	Non-surgical retreatment
PI	Principal Investigator
PT	Previously treated
RCT	Root canal therapy
SPSS	Statistical package for the social sciences
S-Retx	Surgical retreatment
tid	Three times a day
UIC COD	University of Illinois at Chicago, College of Dentistry
VAS	Visual analog scale

1.0 Project Summary/Abstract

The purpose of this study is to evaluate the administration of prophylactic antibiotics on the incidence of postoperative pain, infection, and swelling following endodontic microsurgery. Patients referred for root-end surgery and who are at least 18 years old will be selected and treated in the University of Illinois-Chicago College of Dentistry Postgraduate Endodontics Clinic. Inclusion criteria are as follows: teeth with adequate coronal restoration and a diagnosis of symptomatic apical periodontitis, asymptomatic apical periodontitis, or chronic apical abscess that cannot be predictably managed with nonsurgical endodontic retreatment. Exclusion criteria are: allergy to penicillin or amoxicillin, currently taking antibiotics or methotrexate, kidney disease, phenylketonuria, or dialysis. Other exclusion criteria will be severe periodontitis, acute symptoms of infection such as swelling and fever, patients required to take prophylactic antibiotics for a systemic disease or medical condition and patients that do not speak and understand English. Each patient that meets the inclusion criteria will be randomly given either a placebo or amoxicillin and will have their surgical treatment performed by a second year postgraduate resident. Patients will be instructed to take ibuprofen 600 mg every 6 hours if necessary for pain management. Patients will take two tablets of either 500 mg amoxicillin or placebo 1 hour prior to treatment followed by a 5-day course consisting of amoxicillin 500 mg tid or placebo tid. Postoperative instructions and a visual analogue scale (VAS) for pain will be given to the patient at the completion of the surgery. Pain will be recorded preoperatively and postoperatively at 6, 24, 48, and 72 hours, and on the day of suture removal—typically 4-6 days after surgery—by placing a mark on a horizontal VAS. A 170mm Heft-Parker scale will be used, with 0mm representing no pain and 170mm representing maximum possible pain. Patients will also be asked to record the use of over-the-counter or prescribed pain medication, including frequency, type, and dosage. Infection will be evaluated as either present or absent; the presence of infection will be marked by positive purulent drainage from the incision. The null hypothesis is that there is no significant difference in pain, infection, or swelling when antibiotics are prescribed for endodontic surgery. Dentists regularly prescribe systemic antibiotics in patients who are not immunocompromised or do not have signs of an acute or systemic infection. Furthermore, the endodontic literature lacks high level evidence to either support or reject the use of antibiotics in otherwise healthy patients undergoing endodontic surgery. The significance of this study is that it may help reduce the inappropriate use of antibiotics and possibly decrease the risk of antibiotic resistance. The main goal is to provide preliminary support and justification for a larger scale study on the topic. Based on findings from this pilot study, the protocol may be modified and appropriate sample size calculation should be possible.

2.0 Literature Review/Background

The use of prophylactic antibiotics in surgical endodontics is controversial[1] and there is a growing concern about the over-prescribing and overuse of antibiotics, which may lead to increased frequency of bacterial resistance. The inappropriate use of antibiotics creates a higher risk for possible anaphylactic reactions while exposing the patient to unnecessary side effects[2] such as risk of hospital infection[3]. It also inadvertently creates an increased expectation and dependence among people for antibiotics[2]; thus, it is essential that antibiotics be prescribed only when there are expected clinical benefits. Dentists are the third most common health care provider prescribing antibiotics, with 24.5 million prescriptions written in 2013[4]. In a survey sent to American Association of Endodontists members in 2000, 37% of endodontists routinely prescribed antibiotics for microsurgery[5] despite the recommendation that use of antibiotics should be limited to patients with systemic signs of infection such as cellulitis, lymphadenopathy, swelling, and fever[2]. Of the respondents in the AAE survey, an average of 9.25 antibiotic prescriptions were written per week for varying treatment procedures, some solely on the basis of patient demand, expectations of the referring dentist, or presumed medical-legal reasons. Endodontic surgery is typically performed in situations with a localized area of pathosis and overall healthy tissue. In non-immunocompromised patients and with sterile surgical technique, antibiotics are generally not indicated[5].

Penarrocha showed no significant difference between pre- and postoperative pain following periapical surgery at 7 days postoperatively.[6]. Swelling and pain reached its peak at 2 days postoperatively, however the most pain was observed within the first 48 hours after surgery. Mandibular anterior teeth were found to be associated with the most discomfort whereas maxillary molars and mandibular premolars had the least. Smaller osteotomies less than 1 centimeter were associated with less pain than osteotomies greater than 1 centimeter, however size had no correlation with inflammation[6]. In a study comparing root-end resection using either Mineral Trioxide Aggregate (MTA) or Intermediate Restorative Material (IRM), Chong and Pitt Ford found that within the first 6 hours following endodontic surgery, 90% of patients experienced some level of pain with 37% of patients choosing not to take any form of analgesics. Along with a decline in VAS measurements, there was also a continuous decline in postoperative pain with 82% and 72% of patients reporting discomfort after 24 hours and 48 hours respectively. These findings, however, were statistically insignificant[7].

In a study by Christiansen et al evaluating pain levels following periapical microsurgery in 42 patients with apical periodontitis, there was a significant difference in postoperative discomfort with VAS scores peaking at 3 hours postoperatively. Swelling was at its highest 1 day postoperatively and there was no significant difference in swelling when comparing 1, 2, and 3 days postoperatively. Interestingly, the author found a significantly higher VAS score for pain and swelling among women compared to men 3 hours postoperatively for pain and 1 day postoperatively for swelling. Overall, it was found that there was little discomfort and only moderate swelling following endodontic surgery[8].

The primary etiology of persistent apical periodontitis is microorganisms; the rationale for prescribing pre-operative and/or post-operative antibiotics is that surgical intervention could cause a bacterial infection within the surgical site[1]. There is much controversy on this issue. The use of systemic antibiotics has not been proven to help reduce pain or swelling in cases of apical periodontitis with the absence of systemic involvement[2]. Several studies have shown no significant difference in pain levels between the control and experimental groups. The effective dosage of prophylactic clindamycin for the prevention of postoperative infections following endodontic microsurgery was assessed in a double-blind placebo-controlled trial. Randomly selected patients received 600 mg of clindamycin preoperatively. After a 28-month evaluation with a 100% recall rate, 2 infections had developed in the experimental group and 4 wound infections had developed in the control group, all occurring within the first 2 weeks and presenting as subcutaneous fluctuant swelling. However, there was no statistically significant difference found in regards to the use of prophylactic antibiotics in preventing postoperative infections[1].

There is a lack of double-blind, randomized controlled trials supporting or opposing the use of systemic antibiotics for endodontic surgery[1]. A Cochrane Database Review searched for randomized controlled trials using systemic antibiotics in patients with symptomatic apical periodontitis or acute apical abscess that were treated with either extraction, incision and drainage, or endodontic therapy with or without antibiotics and found two articles that met the specified criteria. Both studies found no statistically significant difference in pain or swelling between the experimental group receiving oral antibiotics compared to the control group receiving the placebo with initial root canal therapy. This review showed that there is insufficient data determining the effects of antibiotics when used for apical periodontitis and that the evidence that is currently available is of low quality[2].

Escalante evaluated the effects of a single dose of 500 mg azithromycin or 2 g amoxicillin prior to one-stage implant placement and discovered patients taking azithromycin had fewer proinflammatory cytokines and chemokines in both the gingival crevicular fluid from adjacent teeth and the peri-implant crevicular fluid[9]. A separate study found that antibiotic prophylaxis had a significant effect in reducing the risk for infection complications in intra-oral bone grafts. Either 2 grams pheneticillin or a placebo was given to 20 patients 1 hour prior to the procedure. Of the 20 patients, 2 developed wound infections at the receptor site, 2 at both the receptor and donor site, and 1 at the donor site within the first 10 days postoperatively. All 5 patients were in the placebo group and all cultures had penicillin-sensitive streptococci present[3].

Dental pain can have a negative effect on a person's quality of life. There are multiple strategies that have been implemented for controlling pain after endodontic therapy. Such strategies include analgesics, occlusal reduction, and long-acting anesthetics[10]. In a study involving 92 patients and 95 single rooted anterior teeth with apical periodontitis, there was significantly more discomfort and swelling within the first 24 hours after endodontic surgery followed by a gradual decrease in intensity for both[11].

This proposed study will evaluate the effect of antibiotics on postoperative swelling, infection, and pain. In a study comparing the duration of antibiotics in orthognathic surgeries there was a significantly higher occurrence of postoperative infections when given 1 day of antibiotics versus 5 days (6.3 times greater incidence of infection in the 1-day group). It was concluded that antibiotic prophylaxis administration should continue for longer than just the immediate postoperative period in order to provide adequate coverage[12]. A Cochrane Database Systematic Review that evaluated the effects of antibiotic prophylaxis in patients undergoing orthognathic surgery pooled 7 trials that administered either a single preoperative dose, a short-term dosage that consisted of antibiotic administration before or during surgery and/or the same day of surgery, and a long-term dosage that consisted of antibiotics before or during surgery and longer than 1 day postoperatively. The search found that long-term antibiotic prophylaxis had a reduction of surgical site infections ranging from 0.26% to 76%. It was concluded that administration or prophylactic antibiotics for more than 1 day postoperatively decreased the risk of surgical site infections in patients undergoing orthognathic surgery compared to a single dose or a short-term dose[13]. In another study involving the management of postoperative endodontic pain with either ibuprofen only or ibuprofen and amoxicillin/clavulanic acid, there was a significant reduction in pain and consumption of NSAIDs in the antibiotic group[14]. The number of adverse reactions to amoxicillin compared to clindamycin was found to be significantly lower in a study evaluating the incidence of reactions when given prophylactically for infective endocarditis in an English population. Data was recorded for prescriptions of either a single oral dose of 2 g amoxicillin or 600 mg clindamycin. For 3 million prescriptions written for amoxicillin, there were zero fatal reactions reported. Furthermore, amoxicillin was associated with 23 non-fatal reactions per million prescriptions written. Clindamycin, on the other hand, was found to have 13 fatal and 149 non-fatal adverse reactions per million prescriptions with most being *Clostridium difficile* infections[15].

There is a lack of evidence in the endodontic literature to either reject or accept the use of prophylactic antibiotics following endodontic surgery. The proposed dosing regimen for amoxicillin is based off of current evidence in similar dental surgical procedures such as orthognathic surgery due to the lack of endodontic references. There have been studies showing evidence of improved effectiveness of systemic antibiotics on the occurrence of postoperative infection when prescribed for more than one day following surgery. The AHA and the ADA have published proposed guidelines on medical conditions that should be treated with prophylactic antibiotics along with its corresponding dosages. However, this study incorporates a long term regimen (more than one day postoperatively). The usual dosage for amoxicillin is 1000mg loading dose followed by 500mg every eight hours for five to seven days[16].

3.0 Objectives/Aims

The purpose of this clinical study is to assess the use of prophylactic antibiotics on post-operative pain, infection, and swelling following endodontic microsurgery.

Objectives:

- Obtain and evaluate pain levels following endodontic microsurgery using a Heft-Parker VAS.
- Evaluate the presence of infection and swelling to determine the success of soft tissue healing.
- Assess whether there is an association between prophylactic antibiotics and postoperative pain, swelling, and infection.

Hypothesis:

$H0_A$: There is no difference in postoperative pain when given amoxicillin prophylactically for endodontic surgery compared to the placebo.

$H1_A$: Amoxicillin reduces postoperative pain levels in patients undergoing endodontic surgery.

$H0_B$: There is no difference in the occurrence of postoperative swelling following endodontic surgery when given amoxicillin prophylactically compared to the placebo.

$H1_B$: Amoxicillin reduces the occurrence of postoperative swelling in patients undergoing endodontic surgery.

$H0_C$: There is no difference in the occurrence of postoperative infection following endodontic surgery when given amoxicillin prophylactically compared to the placebo.

$H1_C$: Amoxicillin reduces the risk of postoperative infection in patients undergoing endodontic surgery.

4.0 Eligibility

Recruitment, treatment and follow-up appointments will be performed between March 1, 2017, through June 30, 2017, in the UIC College of Dentistry postgraduate endodontics clinic.

4.1 Inclusion Criteria

Patients presenting for consultation for surgical endodontic treatment at the UIC Postgraduate Endodontics Clinic who meet the following criteria:

- Age 18 and older
- Tooth with pulpal diagnosis of previously treated, indicating that the tooth has been endodontically treated and the canals obturated with filling materials other than intracanal medicaments
- Tooth with periapical periodontitis or chronic apical abscess

- Non-surgical retreatment root canal therapy is impractical or unlikely to improve on previous treatment due to various reasons such as iatrogenic error (separated instruments, ledges, perforations, strips/zips, overfills), irretrievable material in canals (post/core, silver points, pastes, and cements), or resorptive defects
- Tooth to be treated has an adequate coronal restoration in that there is no clinical or radiographic evidence of marginal leakage or structural breakdown

- Good general health (ASA I or II) with no contraindications to endodontic surgery and no indication for antibiotic premedication prior to surgery (e.g., antibiotic prophylaxis due to increased risk for infective endocarditis; immunocompromised status due to system disease and/or medications)

4.2 Exclusion Criteria

Excluded from the study will be:

- Allergic to penicillin or amoxicillin
- Currently taking antibiotics
- Currently taking methotrexate
- Phenylketonuria, kidney disease or currently on dialysis in which taking amoxicillin would be contraindicated
- Pregnancy
- Severe periodontitis
- Non-English speaking patients
- Acute symptoms of infection
- Prophylactic antibiotics indicated for a systemic disease or medical condition stated by the current ADA guidelines such as patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair, history of infective endocarditis, cardiac transplant that develops cardiac valvulopathy, and congenital heart disease including unrepaired cyanotic congenital heart disease (palliative shunts, conduits), completely repaired congenital heart defect with prosthetic material or device during the first six months after the procedure, and any repaired congenital heart defect with residual defect at the site or adjacent to the site of a prosthetic patch or a prosthetic device

5.0 Subject Enrollment

The study sample will be selected from the pool of patients receiving treatment in the Postgraduate Endodontics Department at the UIC COD. If the patient is seeking treatment on a previously treated tooth that has adequate coronal coverage and obturation with apical periodontitis or chronic apical abscess, treatment options will be discussed including non-surgical retreatment (NS-Retx), surgical retreatment (S-Retx), extraction, and no treatment. If the patient elects surgical treatment, the PI will be notified to discuss details of the study. No other form of recruitment will be performed by an other postgraduate resident other than solely identifying subjects and advising the PI to determine eligibility (checklist provided) and explain the study. The patient will be

provided with a verbal explanation of the study. No other recruitment forms will be provided. Verbal and written informed consent for participation in the study will be obtained by the PI. No data will be recorded for patients that elect not to participate in the study except a one sentence note in the EHR: “Patient declined to participate in study of prophylactic antibiotic use in endodontic microsurgery.” The screening checklist will not contain any PHI and will be shredded at the end of the appointment. The voluntary nature of the study will be emphasized during discussion and the consent process. Although some of the subjects will be treated by the PI, most will be treated by other postgraduate residents that have no interest in the study outcome. Supervising faculty will ensure that no undue influence is applied during the recruitment process. The PI and faculty sponsor have no financial interest in the performance or outcome of the study.

6.0 Study Design and Procedures

All patients will be screened and recruited from those referred for treatment to the University of Illinois at Chicago College of Dentistry Postgraduate Endodontics Clinic between March 1, 2017 and June 30, 2017. All human subject protocols and consent forms will be reviewed and approved by the Institutional Review Board of the University of Illinois at Chicago prior to subject screening and enrollment.

The PI will be notified by an endodontic resident of a patient presenting for consultation in which S-Retx is deemed a viable treatment option following clinical and radiographic evaluation. If the patient elects S-Retx, the patient will be approached by the PI to evaluate inclusion criteria. All participants will be given written and oral information about the study. Patients will sign a written consent and be given the option to opt out of the study at any time. Each patient that meets the inclusion criteria will have their treatment performed by a second year postgraduate resident following the standard of care protocol for modern endodontic microsurgery. Patients will be instructed to take ibuprofen 600 mg every 6 hours if deemed necessary following the procedure. Patients will also be given Vicodin as a rescue medication. Either two tablets of 500 mg amoxicillin or placebo will be taken 1 hour prior to treatment and 1 tablet of the randomly chosen drug for 5 days tid postoperatively. Envelopes labeled with an identification number will be assembled by the University of Illinois Pharmacy and randomly allocated so that patients, provider, and investigators will all be blinded. Only the PI and faculty sponsor will have access to the coded identification numbers in case a medical need arises to break the code and determine if a subject has been taking the active medication or placebo. Postoperative instructions and a VAS for pain will be given to the patient at the completion of the surgery. Pain will be recorded preoperatively at time of written consent and at 6, 24, 48, and 72 hours following treatment, as well as on the day of suture removal— 4-6 days after surgery—by placing a mark on a 170 mm horizontal VAS. Specified measurements correspond to intensity of pain; patients will be provided a scale without numerical correlation. A template will be used by the PI at the completion of the study to record the correlation of intensity of pain to the measurement at which the patient has marked on the Heft-Parker scale. Measurements for both groups will be analyzed at each time interval to determine

whether there is a significant difference in postoperative pain control with the administration of prophylactic antibiotics. This will provide information to help determine whether there is a justified rationale for the administration of antibiotics during endodontic microsurgery. Patients will also be asked to record any consumption of self-prescribed pain relievers, how often, the type, and dosage to assess the effectiveness of prophylactic antibiotics in regards to endodontic pain management. This will be reported as descriptive data only since it is difficult to standardize this type of data. Infection will be evaluated as either present or absent at the date of suture removal; the presence of infection will be marked by positive purulent drainage from the incision, induration, and/or fever. Swelling will be evaluated during the suture removal visit as well and will be categorized as: no inflammation, mild inflammation, or moderate inflammation. Mild inflammation is signified by intraoral swelling confined to the surgical field whereas moderate inflammation involves extraoral swelling in the region of treatment.

Prospective data including information related to pain, swelling, and infection following surgery will be collected but not contain PHI nor will it be linked directly to the subject's EHR. Information regarding patient demographics and any materials used such as bone grafts or membranes are standard information already included within the patients' EHR. Only the PI and faculty sponsor will have access to the information that pertains to the study; this information will be kept in a locked cabinet and securely shredded at the completion of the study. A unique identification number will be used to pair the patient's EHR with all postoperative measurements and questionnaires.

7.0 Expected Risks/Benefits

Expected risks to subjects are minimal. Potential risks following endodontic microsurgery include delayed bleeding, infection, swelling, pain, bruising, and delayed healing. Potential risks associated with the purpose of the research study include risk of infection, loss of confidentiality and privacy, and adverse or allergic reactions to the oral antibiotic given. This includes nausea, vomiting, diarrhea, abdominal pain, and skin reactions. If an unknown adverse reaction occurs, the medication will be immediately discontinued and the patient will be excluded from the study. The knowledge taken from this study has many potential benefits. If the null hypothesis is confirmed, the benefit to society would be reduction in the inappropriate use of antibiotics and thus the decreased risk of antibiotic resistance. If the alternative hypothesis is confirmed, the study would provide support for additional studies and the use of preoperative antibiotics for endodontic microsurgery.

8.0 Data Collection and Management Procedures

Prior to the surgical procedure, subjects will place a mark on the VAS corresponding to current level of pain. After the procedure, subjects will be given a VAS and instructed to record pain level at 6, 24, 48, and 72 hours, as well as on the day of suture removal 4-7

days later by placing a mark on a horizontal VAS. Patients will also be asked to record any consumption of over-the-counter or prescribed pain medications, how often, the type, and dosage. Infection will be evaluated as either present or absent at the date of suture removal; the presence of infection will be determined by positive purulent drainage from the incision, induration, and/or fever. Swelling will be evaluated during the suture removal visit as well and will be categorized as no inflammation, mild inflammation, or moderate inflammation. Mild inflammation pertains to intraoral swelling confined to the surgical field whereas moderate inflammation involves extraoral swelling in the region of where treatment was performed. Data forms will be collected when the subject returns for the suture removal appointment. The data collection forms will be stored in a locked file cabinet in the faculty advisor's locked office, separate from the code numbers that can be linked to the subject's EHR. Only the PI and faculty advisor will have access to the forms.

9.0 Data Analysis

After all data is collected, the code will be broken to determine which subjects received placebo and which received an antibiotic. The de-identified data will then be entered into a statistics software program (SPSS) and analyzed using t-test (for VAS data) and Chi square (swelling and infection). Since this is a pilot study, a formal sample size calculation was not performed. Data analysis from this study will form the basis for sample size calculation for a subsequent expanded version of this study.

10.0 Quality Control and Quality Assurance

The PI and faculty advisor will provide continuous monitoring of any adverse or unexpected reactions during the course of the study. Any adverse reactions will be noted and treated appropriately. In the unlikely event that adverse reactions are noted at a rate higher than normally expected following endodontic microsurgery (typically less than 10 to 20% for minor adverse events, and less than 1% for potentially serious events), the research will be halted, a complete review will occur, and a report will be submitted to the IRB.

11.0 Regulatory Requirements

Informed Consent

Informed consent specifically designed for the research study will be presented to each participant who expresses a willingness to participate. Verbal consent will be given at the time of consultation. Written consent will be provided on the day of treatment. Signature consenting to participation in the study will be required for inclusion in the study. The PI will be responsible for obtaining informed consent. All consent forms will be provided in English. The PI will be trained on evaluating participant eligibility and obtaining necessary informed consents.

This study imposes minimum risk to participants and there are no anticipated problems or adverse reactions. Unanticipated problems will be managed according to standard protocol and will be evaluated to determine whether or not the adverse event could have been related to participation in the study.

VITA

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