A PILOT STUDY EVALUATING THE EFFECT OF COLLAGEN SPONGES ON HEALING AND PAIN FOLLOWING TOOTH EXTRACTION

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MASTERS OF SCIENCE

by

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ABSTRACT

Background: Clinicians often use collagen-derived matrices to aid in the regeneration of periodontal tissue during periodontal therapy; other uses of these materials include clot stabilization, wound protection, and patient comfort. The primary objective of this study is to evaluate the effect of absorbable collagen matrices on post-operative healing and pain.

Materials: Five patients requiring multiple extractions were enrolled in a split mouth study design. Each subject required extraction of two or more similar sized teeth. The same nerve division with contralateral afferent terminations innervated each pair. We randomly assigned subjects to either a control or experimental group via a coin toss. The experimental groups received collagen sponges while the control groups received extraction only. All patients documented their pain experience in provided journals. In addition, calibrated examiners measured the wound margin closure via photographs of the extraction socket with a University of
North Carolina probe as reference for measurement. Each examiner recorded the wound margins at baseline, three, seven, and twenty-one days following the extraction. Statistical analysis of the pain score and closure rates were conducted to determine results.

Results: Five female patients were enrolled in the study, four of which were in active orthodontic treatment. Sixteen sites were measured, eight control and eight experimental. The general trend over time was that the collagen group had a higher rate of wound margin closure than the control, however statistical analysis indicated no significant difference (p > .05). In contrast, the average pain as reported on the numerical rating scale (NRS) was higher for the experimental side, although statistical analysis indicated that the difference was not significant (p > .05).

Conclusion: The use of collagen sponges in extraction sockets do not increase the rate of wound margin closure. In addition, the use of collagen sponges does not decrease post-operative pain following a tooth extraction.
The faculty listed below, appointed by the Dean of the School of Dentistry have examined a thesis titled “A Pilot Study Evaluating the Effect of Collagen Sponges on Healing and Pain Following Tooth Extraction,” presented by Bahman Norouzinia, candidate for the Master of Science degree, and certify that in their opinion is worthy of acceptance.

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CHAPTER 1
INTRODUCTION

Synthetic and organic collagen is commonly used as an adjunct in regenerative periodontal therapy. The biocompatibility and widespread application of collagen sponges attribute to its use in periodontics. Collagen comes in various forms and can be indicated for hemostasis or as a bioresorbable membrane (Bunyaratavej and Wang 2001). Type I collagen is abundant in bone, tendons, skin, ligaments and other tissue types of mammals (Patino et al. 2002). Collagen can be classified into fibrillar or nonfibrillar collagen types, which are designated by Roman numerals. Currently, most collagen membranes used in dentistry are procured either from bovine or porcine donors and may contain either type I or type III collagen (Kao 2004). An equine form of collagen is used in wound dressings as well. Specifically, collagen sponges have been advertised to control bleeding, protect the wound bed, facilitate the healing process, stabilize the clot, and aggregate clotting factors. In some studies they have been used for tissue exclusion (Kim et al. 2011) and are thought to resorb within ten to fourteen days. The membrane’s bioresorbable property comes from the actions of collagenase, gelatinase, and peptidase (Kao 2004). Because of advancements in dental therapy and biomaterials, the prognosis of most dental treatments has improved. However, the inevitable and final treatment of an unrestorable tooth remains a dental extraction. As a result, dental extractions remain a prevalent treatment in the dental practice (Presson et al. 2000). As with any treatment, side effects and complications
can arise, such as alveolar osteitis and ridge resorption. Alveolar osteitis is better
known as “dry socket,” and is characterized by severe pain usually occurring 48-72
hours after the procedure. Although dry socket has a reported prevalence rate of 2-
3% (Heasman and Jacobs 1984) it is a complication with a significant increase in
patient morbidity and therefore clinicians attempt to minimize its occurrence.
Subsequent to dental extractions, the alveolar process progressively changes
resulting in a resorbed alveolar ridge (Schropp et al. 2003; Araujo and Lindhe 2009).
These ridge alterations can influence the clinician’s decision for prosthodontic
rehabilitation making it important to understand the process and maintain the ability
to manipulate the outcome to the patient’s and practitioner’s advantage. Different
techniques and materials have been utilized to decrease post-extraction ridge
changes and common to all methods is the philosophy of epithelial exclusion. Using
a resorbable collagen sponge is one such method. Although most studies assert
that collagen sponges enhance the healing process by stabilizing a clot, some
authors elude to their use in epithelial exclusion (Kim et al. 2011).

The Healing Alveolar Socket

Early reports of the healing alveolar socket generalize the process to a five
stage healing sequence.

(1) clot formation; (2) replacement of blood clot by granulation tissue (seventh
day); (3) replacement of granulation tissue by connective tissue (twentieth
day); (4) appearance of osteoid at the base of the socket (seventh day) and
filling of at least two thirds of socket fundus by trabeculae (thirty-eighth day),
and (5) evidence of epithelization (fourth day). (Amler et al. 1960)
Healing occurs almost immediately after the extraction when the formation and organization of the blood clot begins. After the socket fills with blood, hemostasis is achieved and the coagulation process is complete. The gingival tissue that remains after the extraction encourages the healing process by collapsing over the socket and partially occluding the opening of the socket (Simpson 1968). Underneath this wound margin the coagulum that is formed in the first 24 hours is replaced partly by granulation tissue, while in a more apical zone the clot is replaced by mesenchymal cells and erythrocytes (Cardaropoli et al. 2003). It is suggested that the formation of granulation tissue is in response to the presence of infectious material in the oral cavity and the inflamed tissue serves as a barrier to protect the more apical parts of the alveolus” (Cardaropoli et al. 2003). New vessel formation then begins from the socket walls with approximately half of the remaining PDL forming an uneven thickness with blood vessels seen in the PDL (Simpson 1968). In addition, Cardaropoli also demonstrated that the “severed PDL was found to contain large numbers of mesenchymal cells, fibers and a multitude of large apparently dilated vascular units” (Cardaropoli et al. 2003). Although most of these histological findings were reported in rats, dogs, and monkeys (Devlin and Sloan 2002) found similar results in humans. In that particular study, they demonstrated an organization of a fibrin blood clot which was replaced by fibrous tissue and blood vessels within the first 4 weeks after the extraction. The production of osteoid and its inevitable remodeling can be observed first from the alveolar walls (Simpson 1968). “Osteophytes grow out into the socket from the walls and base by a process
of arborisation and extend towards the socket mouth and fill the socket in 3-5 weeks in animals and 15 weeks in man according to Mangos (1941)” (Simpson 1968). Between the first and second month after extraction, osteogenic tissue proliferates and trabecular bone is formed and later matures (Evian et al. 1982). For dogs, the organization and healing process of the socket is as follows. During the initial phase of healing (day 1-3), a blood clot will form which is then replaced by vascularized granulation tissue. After seven days, the granulation tissue matures to a provisional matrix (connective tissue inhabited by mesenchymal cells). By day 14 this matrix develops into woven bone that will mineralize approximately two weeks later (Cardaropoli et al. 2003).

**Post-Extraction Ridge Alterations**

Subsequent to the healing process of an extraction site, the alveolar ridge undergoes changes that result in osseous atrophy (Atwood and Coy 1971). This resorption process typically leads to a greater loss in ridge width than height (Johnson 1969; Schropp et al. 2003). Although this process takes several months, the majority of the loss occurs within the first month following the extraction. Other authors have demonstrated that the majority (two-thirds) of the bone loss occurs within the first three months following the extraction and can result in approximately 50% of bone width loss (Schropp et al. 2003). In addition, Schropp concluded that there was an average vertical bone loss of 2-4.5 mm. Post extraction ridge reductions can have a detrimental effect on future prosthodontic treatment. This
reduction of alveolar bone can preclude the placement of implants or influence the esthetic success of a fixed or removable prosthesis.

**Pain Management**

Pain is often noted following dental extractions. Pain is described by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Because of the broad and ambiguous definition of pain set by the IASP, accurately evaluating a patient’s perception of pain can be difficult. In order to better evaluate this perception, Melzack attempted to categorize the psychological dimensions of pain into the following: sensory, affective, and evaluative (Melzack 1975). He hypothesized that these categories interact with one another to provide quantitative and qualitative information on the components of pain. From this research, Melzack developed the McGill pain questionnaire in order to evaluate the qualities of pain which has been cited to be a reliable and applicable questionnaire (Mystakidou et al. 2002). Since the perception of pain can dictate one’s attitude regarding treatment, the role of pain management has become increasingly more important. Post-operative pain is generally managed through the adjunctive use of opioids or analgesics and on many occasions a combination of the two. Studies have demonstrated that a combination of opioids and analgesics are more effective in pain relief than stand-alone use (Hellman et al. 1992). The subjective nature of pain allows it to be influenced by many factors, making it a challenge to objectively quantify pain management. As a result, every study has a
different method of collecting and analyzing data for efficacy of pain management. However, common to most studies is the concept of a visual analog scale (VAS). This method uses a visual scale as a reference for patients, which is based on a 10-centimeter scale that has two extreme endpoints that are anchored by verbal descriptors such as no pain and worst pain. (Petersen et al. 1993; Roelofse and Payne 1999; Ziccardi et al. 2000; Bhaskar et al. 2010). Although the VAS has been cited as being accurate when compared to other scales (Ohnhaus and Adler 1975) its use in repeated measurements with short intervals, result in 90% of the values scored within a short distance to each other (Bijur et al. 2001). The advantage of the VAS over a numerical rating scale (NRS) is its ability to have more levels of discrimination. However, this may be excessive for such a broad and subjective variable as discussed by Jensen. He determined when a 101-point scale was utilized for quantifying pain; most patients document their scores at increments of either 10 or 5. These multiples when analyzed on a 100 millimeter VAS resulted in 11 or 21 points of discrimination (Jensen et al. 1994). Considering this, the VAS scale becomes a more complicated and unnecessary scale of measurement. As concluded by Williamson and Hoggart, “The Numerical Rating Scale has good sensitivity and generates data that can be statistically analyzed for audit purposes” (Williamson and Hoggart 2005). Once the raw data is obtained from the pain scale, changes in pain intensity can be measured directly by the patient or calculated by the percentage of pain reduction (pre-score subtracted by post-op score /pretreatment score) (Farrar et al. 2000). The overall effectiveness of pain
management has been cited in the literature as a 30% reduction in pain (Farrar et al. 2000). Additionally, studies also employ the use of “rescue” medications (Farrar et al. 2000). These are taken when the control or test variables are insufficient in pain control. Although this is not utilized as a direct diagnostic analysis, it could be applied as an objective verification for the need of pain management, and indirectly the effectiveness of the variable being tested. Inflammatory cytokines are released during tissue injury to isolate the wound site and initiate the healing process. These chemical signals result in the five classic signs of inflammation and subsequently pain associated with inflammation. By decreasing the wound repair time, inevitably you would also decrease the duration of inflammation and pain. This is the concept behind reducing pain in the extraction socket with the use of collagen sponges. By using the NRS, we can objectively infer the effects of collagen sponges on postoperative pain.

**Tissue Engineering**

The alveolar ridge alteration described by Schropp and Atwood have prompted clinicians to preserve the ridge (Atwood and Coy 1971; Schropp et al. 2003). The process of tissue engineering and ridge preservation encompass the utilization of three main concepts: (1) signaling molecules, (2) scaffolding material, and (3) guided tissue regeneration. Employing scaffolding materials in tissue engineering can accomplish any of the following: (1) provide physical support to the area, (2) serve as a barrier, (3) allow for cells to migrate and proliferate through the scaffolding material, and (4) serve as a release mechanism for signaling molecules
Classically bone replacement grafts have been the treatment of choice to facilitate regeneration of osseous defects. These grafts may be autografts, allografts, alloplasts, or xenografts (Tissue banking of bone allografts used in periodontal regeneration 2001; Reynolds et al. 2003). Collagen carriers are also among the scaffolding materials of choice. Although not primarily used for scaffolding, many authors have alluded to its potential use. Since collagen is a major component of tissue support, their role in wound healing has been essential, specifically they provide a biologic scaffold for cellular migration and proliferation (Kao et al. 2009) and may be used in tissue engineering by seeding mesenchymal stem cells (Juncosa-Melvin et al. 2006). In addition to seeding precursor cells and providing a scaffolding, studies have also reported collagen’s ability to act as a barrier. After a tooth has been extracted atraumatically the resulting five wall (barring there were no previous defects) defect allows any grafting material to be placed and stabilized. This stabilization allows for the use of a collagen sponge as a barrier membrane thus utilizing the concept of guided tissue regeneration.

**Problem Statement**

No experimental studies have been conducted on the effects of collagen sponges in extraction sockets. More specifically, the possible beneficial effects of collagen sponges on wound margin closure, patient’s post-operative pain, or alveolar remodeling of the socket. The effects of collagen on extraction sockets are valuable because preservation and remodeling of the socket could potentially be advantageous for future prosthodontic strategies. Decreased wound healing can
lead to chronic inflammation and increased post-operative complications and pain. In addition, epithelial migration into the socket can occupy and limit the amount of bone fill, subsequently resulting in alveolar and soft tissue contour changes that can create prosthodontic challenges. Unfortunately, due to time constraints we were unable to measure the effects of the material on the preservation of the socket. Instead, we limited the study to evaluate its effects on soft tissue healing and post-operative pain following atraumatic tooth extraction.

**Hypotheses**

1) The use of collagen sponges in extraction sockets will increase the rate of wound closure. 2) The patient’s postoperative pain will be significantly decreased when utilizing the collagen sponge.
CHAPTER 2
MATERIALS AND METHODS

Collagen Sponges

The collagen sponges used in this study are based on their use in extraction sockets to establish a blood clot. The composition of this particular collagen sponge (Zimmer Collaplug®) is made up of type I bovine collagen derived from the Achilles tendon. Its dimensions are 10 mm X 20 mm and have a resorption period of 10-14 days. The company indicates its use for the following: 1) control bleeding, 2) stabilizing the blood clot, and 3) protecting the wound bed.

Instrumentation and Measurements

The study was reviewed by the Adult Health Sciences Institutional Review Board of the University of Missouri Kansas City and granted approval. The criteria for inclusion and exclusion of study participants are listed below.

Patient Inclusion Criteria

Patient inclusion criteria were as follows: 1) Extraction of two similar sized teeth on contralateral sides of the jaw or in an area innervated by different nerve division; 2) Is an English speaking patient; 3) Belongs to American Society of Anesthesiology (ASA) classification of I, II or non-complicated III; 4) The teeth to be extracted must have a minimum of 50% of periodontal support; 5) Does not reject the use of a xenograft material; 6) Alveolar sockets that are not severely dehisced.

1 Zimmer Collaplug®, Integra Life Sciences Corp, 311 Enterprise Dr., Plainsboro, NJ, 08536.
<5mm; and 7) Patients that have taken oral bisphosphonates will be included in the study.

**Patient Exclusion Criteria**

Patients excluded from the study include those who: 1) exhibit uncontrolled systemic disease or immune suppression; 2) require antibiotic prophylaxis; 3) are allergic to NSAIDS or medications used in post-operative management; 4) exhibit ankylosed dentition or iatrogenic complications as a result of surgery (this would include creating critical sized defects during surgery, for example buccal plate fractures); 5) received radiation therapy to the head and neck; 6) are pregnant; 7) third molars; 8) are less than 18 years of age; 9) have taken intravenous bisphosphonates; and/or 10) exhibit a dehiscence of > 5mm discovered during the extraction (the patient’s data will be discarded from the study).

**Protocol Overview**

All extractions were simple extractions performed with a combination of proximators, elevators, and forceps. Healing rates were measured in millimeters of wound closure per day. Examiners measured the distance by placing a University of North Carolina (UNC) periodontal probe over the socket in both buccal-lingual and mesial-distal directions. A photograph was then taken of the socket with the probe in place (fig. 2). The photographs were taken on the day of the extraction (baseline), three days, seven days and twenty-one days post-extraction. These photographs were used to determine the distance between the wound margins.
The calibration of the examiners was conducted by two different methods. For the intra examiner reliability, each examiner recorded a set of measurements from a series of photos; the photos were then re-recorded nine months later. These photos were from different healing points and from different patients. The re-measured values were tested against the examiners’ previous measurement to determine intra examiner reliability. These examiners were tested by Pearson's coefficient, Cronbach’s alpha and intraclass correlation coefficient (ICC) for intra and inter examiner reliability. To determine inter examiner reliability, the clinical measurements were evaluated to the nearest 0.5mm and tested by a Pearson’s correlation test.

Patients were assigned a journal to document their pain experience and medication use. Each journal was designated with the letter L or R to represent the designated experimental group. The decrease in post-operative pain was determined by a numeric rating scale (NRS) (Williamson and Hoggart 2005) (Appendix A). The scale is attached to two endpoints indicating the extremes of pain experience. There were two groups of NRS for each day; one corresponds to the control and the other the experimental group. We did not disclose the identity of the experimental side to the patients. The patients recorded their baseline pain perception prior to the treatment procedure. After recording their baseline pain, they were instructed to document their pain experience for different time points, in the morning, mid-day, and before bed. Patients were informed on proper documentation of their pain experience via written and verbal form.
Non-steroidal anti-inflammatory medications (NSAIDS) (Ibuprofen over the counter) were provided at 200 milligrams X three tablets every six hours for three days. This was to counteract the initial inflammatory phase. After the initial inflammatory phase, patients were instructed to only take medications as needed.

**Surgical Protocol**

Both extractions were performed at the same appointment. A coin flip determines which half of the patient will receive the experimental group. The right side will always be designated for the coin toss, if the coin lands on heads then the right side will receive the collagen sponge, if it lands on tails then it will be the control. The patient will then rinse with 15 milliliters of 0.12% Chlorhexidine Gluconate for 30 seconds and then expectorate. All extractions were performed atraumatically under local anesthesia with the use of a proximator. Sockets were rinsed with sterile water. One collagen sponge is then placed in each individual socket and covered with a superficial layer of collagen. The collagen sponges were then sutured over with 4.0 polyglycolic acid (PGA)\(^2\) sutures. Post-operative instructions were given via written and verbal form (Appendix C). In order to reduce inflammation and plaque accumulation, patients were instructed to rinse with 0.12% Chlorhexidine Gluconate rinse (Sanz et al. 1989).

\(^2\) A-Titan Instruments, 97 Main Street, Hamburg, NY, 14075.
**Experimental Design**

A randomized split mouth study was conducted to limit external confounding factors. The experiment is an in-vivo clinical trial which utilizes a two factor repeated measurement design. The first independent variable is the wound margin closure rate and it will consist of two levels. This includes the use of a sponge and the absence of a sponge. The second independent variable is the post-operative pain, which consist of two levels, the use and absence of a collagen sponge.

**Statistical Analysis**

Each patient had either two or four teeth extracted. Each pair of teeth extracted was considered as one subject. Some patients required multiple extractions, and each pair of extracted teeth was treated as one subject within data analysis. Thus, an individual with four extracted teeth was treated as two subjects during statistical analysis. Three of five patients were analyzed in this way (table 1). The same nerve division and branches innervated all subjects; however, they were on contralateral sides. A repeated mixed factor analysis of variance (ANOVA) was conducted to investigate the effect of collagen sponge on marginal wound closure rate and post-operative pain over three-time points post-extraction. The time points were at baseline, three days, seven days and twenty-one days. Collagen sponge was treated as both a within and between subjects factor given that each subject was randomly assigned to both conditions (one tooth per condition) and thus, acted as their own control. A follow-up repeated measures ANOVA analysis was also conducted with smoking status of the individual added as a between-subjects factor.
We sought to determine if smokers and non-smokers differ over time in terms of rate of closure and success with type of treatment (i.e. collagen sponge vs. not treatment). Figures 4 and 5 provide visual illustration of the effects of the socket material on marginal wound closure rate and post-operative pain. We also ran effect size (partial eta squared) for pain and wound closure. Data analyses were conducted with IBM SPSS Statistical Software Programming.\textsuperscript{3}

\begin{table}[h]
\centering
\caption{SUBJECT DISTRIBUTION BY PATIENT}
\begin{tabular}{|c|c|}
\hline
Patient # & Subject # \\
\hline
1 & 1 \\
\hline
2 & 2 \\
\hline
3 & 3 & 4 \\
\hline
4 & 5 & 6 \\
\hline
5 & 7 & 8 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{3} Statistical package for the social sciences (SPSS) version 20, IBM Inc., Armonk, NY, 10504.
Five out of five patients completed the study. Four of the five patients were in active orthodontic treatment at the time of extraction and required multiple extractions. This yielded five patients with 16 extraction sites (table 2). All participants were female, ages 20-57 (M=35.6; SD=16.3). Twelve of 16 teeth were extracted from individuals who were non-smokers.

### TABLE 2

**DISTRIBUTION OF TEETH**

<table>
<thead>
<tr>
<th></th>
<th>1(^{st}) premolar</th>
<th>2(^{nd}) premolar</th>
<th>Central Incisor</th>
<th>Lateral Incisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxilla</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mandible</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Pain Management

As expected, there was a significant main effect of pain, which revealed that pain decreased over time. By day 14, patients reported no pain. Means and standard deviations of average pain ratings are reported in table 3. Results of the repeated mixed factor ANOVA revealed that there were no significant differences in pain ratings between experimental and control conditions (listed in table 5). However, the control group showed a trend of less pain than the experimental group (see table 3 and fig. 1 below). An analysis of effect size (partial eta squared= .082) revealed that use of the collagen sponge accounted for 8.2% of the variability in pain among patients.
TABLE 3
MEANS AND STANDARD DEVIATIONS OF DAILY PAIN

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
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</tr>
<tr>
<td>Experimental</td>
<td>6.45</td>
<td>3.66</td>
<td>6.17</td>
<td>2.44</td>
<td>6.25</td>
<td>2.93</td>
<td>6.17</td>
<td>2.77</td>
<td>5.04</td>
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<tr>
<td>Control</td>
<td>4.96</td>
<td>3.91</td>
<td>4.21</td>
<td>4.07</td>
<td>4.08</td>
<td>3.78</td>
<td>3.79</td>
<td>3.90</td>
<td>3.42</td>
</tr>
</tbody>
</table>

Note: Data was obtained from participant responses to a numerical pain rating scale. Pain was rated on a scale of 1 to 10, with a score of 1 indicating zero pain.
Wound Closure

Wound margin closure rates were compared utilizing photographs with the UNC probe in place (fig. 2). The average initial wound margin distance for both the control and experimental groups in a buccal lingual direction (BL) were 5.90mm SD=1.74 and 6.15mm SD=2.00 respectively, while the average distance in a mesial distal (MD) direction was 5.02mm SD=1.33 and 5.21mm SD=1.76. This resulted in a BL difference of 0.25mm and a MD difference of 0.19mm. Therefore, the initial defect size between the experimental and control groups were similar.

Figure 1. Pain rating between the control and experimental groups
As expected, there was a significant main effect of closure rate over time such that patients experienced significant advances in healing from measurement immediately following surgery to the final day of follow-up. Means and standard deviations of wound closure post-operatively are shown in table 4. A repeated mixed design ANOVA was conducted to determine differences between the experimental and control group. The mixed design ANOVA showed that there were no significant differences between treatment and control in terms of closure rate (see table 5). The general trend over time was that the collagen group had a slightly higher rate of wound margin closure (fig. 3). For wound closure, the collagen sponge effect size was 0.011 indicating that 1.1% of the difference in wound closure rates between the groups was due to the collagen sponge.
# TABLE 4
MEANS AND STANDARD DEVIATIONS OF CLOSURE RATES

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Experimental</td>
<td>0</td>
<td>0</td>
<td>0.525</td>
<td>0.41</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>0</td>
<td>0.46</td>
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</table>

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<th>Day 3</th>
<th>Day 7</th>
<th>Day 21</th>
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<td></td>
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<td>SD</td>
<td>M</td>
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</tr>
<tr>
<td>Experimental</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MD</td>
<td>0.47</td>
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<tr>
<td>Control</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>MD</td>
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21
Figure 2. Clinical measurement mesial distal direction (MD)

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closure Rate</td>
<td>F(1.43) = .186</td>
<td>.757</td>
</tr>
<tr>
<td>Pain</td>
<td>F(2.30) = .803</td>
<td>.473</td>
</tr>
</tbody>
</table>
Smokers vs. Non-Smokers

Means and standard deviations for average wound closure stratified by smoking status are listed in table 6. A repeated mixed factor ANOVA revealed a significant main effect of smoking status such that individuals who were non-smokers healed significantly faster than those who smoked (table 7). Given that smoking has been shown to negatively affect healing, we ran separate analyses (repeated measures ANOVA) based on smoking status. With the smoking patient removed, an analysis of effect size revealed a large effect of the collagen sponge on
wound closure (partial eta squared= .26). Repeated measures ANOVA revealed that there were no significant differences within groups for collagen sponge versus control treatment (p> 0.05). However, examination of means within groups revealed that a trend for slightly improved wound closure with collagen sponge among non-smokers (figure 4). Conversely, the patient who smoked showed a trend of improved healing in control extraction sites (figure 5).

TABLE 6
MEANS AND STANDARD DEVIATIONS OF CLOSURE RATE SEPARATED BY SMOKING STATUS OF PATIENT

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
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<td>SD</td>
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<td>SD</td>
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<td>SD</td>
</tr>
<tr>
<td>Experimental</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Non-smoker</td>
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<td>0</td>
<td>0.71</td>
<td>0.2</td>
</tr>
<tr>
<td>Smoker</td>
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<td>0</td>
<td>-0.03</td>
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</tr>
<tr>
<td></td>
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<td>0.02</td>
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<td></td>
<td></td>
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<td>0.13</td>
<td>0.007</td>
</tr>
<tr>
<td>Control</td>
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</tr>
<tr>
<td>Non-smoker</td>
<td>0</td>
<td>0</td>
<td>0.52</td>
<td>0.2</td>
</tr>
<tr>
<td>Smoker</td>
<td>0</td>
<td>0</td>
<td>0.29</td>
<td>0.13</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.17</td>
<td>0.007</td>
</tr>
</tbody>
</table>
TABLE 7
MIXED-DESIGN ANOVA OF SMOKING STATUS AND INTERACTION EFFECTS

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking Status</td>
<td>F(1)= 44.01</td>
<td>.000</td>
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</tbody>
</table>

Figure 4. Wound closure rate of smokers and non-smokers
Figure 5. Comparing closure rate of collagen sponges and standard treatment in smokers
Figure 6. Comparing closure rate of collagen sponges and standard treatment in non-smokers
CHAPTER 4
DISCUSSION

This experiment examined the effect of collagen sponges on wound closure and pain following extraction within and between subjects. Analyses showed that there were no significant differences between collagen sponges and control sites on pain or post-operative healing rate. However, there was a significant effect of smoking status on wound closure rate. A discussion of these results, limitations and future directions are discussed below.

Wound Closure

In terms of wound closure rate, the experimental group showed a trend of a higher rate of closure than the control; however this was determined to have no statistical significance (p >0.05). Although in our study collagen sponges did not add any benefit to the patient’s rate of healing, our study was a pilot project and we cannot make any definite conclusions at this time. In addition, our study did not investigate the effects of the collagen sponge on ridge remodeling or preservation. This pilot may suggest that the early wound closure rates of the collagen group could potentially have an effect on the ridge composition during healing and should be considered as an aspect for further investigation.

Pain

Our analyses revealed there was no significant pain decrease with the collagen group. At this time, it remains unclear why those in the treatment group reported a trend of more pain. Due to the subjective nature of pain, it can be very
difficult to interpret the results. Many confounding factors that limit the interpretation of pain were taken into consideration; one simple example is sex and gender differences. With respect to these two terms, it is important to address the issue of terminology. The term gender is used to describe a socially supported phenomenon, ex: masculinity and femininity while the term sex is reserved for biological differences (Greenspan et al. 2007). Differences in the sex of subjects can have varying effects on data collection. The current presumption is that females have a higher sensitivity to pain when compared to males. In addition to perceiving pain differently, male and females have different biological compositions, for example they may have differences in distribution of adipose tissue and even different rates of hepatic metabolism (Shapiro et al. 1995). All of these factors can have an effect on pain interpretation, especially if a hepatically metabolized pharmaceutical agent is utilized for pain management. Other factors that might contribute to pain interpretation include ongoing dental treatment, in the example of our patients, orthodontic treatment. One reported study suggests that 91% of adult patients report appliance-induced pain (Lew 1993). Coincidently, in our experiment, all five patients were female, this allowed for the elimination of sex as a confounding factor on pain interpretation. Four of the five patients were in active orthodontic treatment during the dental extractions (day 0). Although this may have contributed to their incidence of pain (Lew 1993), both the experimental and control sites were exposed to similar conditions. Future studies should examine larger sample sizes and possibly examine pain between subjects.
Smoking Status

Collagen matrices are frequently used in periodontal procedures to stabilize clots, form barriers, or act as carriers (Patino et al. 2002). Although these materials are commonly used in periodontal procedures, the literature review on the material remains deficient. In this inquiry, we explored the effect of collagen sponges on patients’ post-operative healing rate and pain. We found that the material does not decrease the patient’s pain experience nor does it significantly increase the healing rate; however, the results of the healing rate were not the same when patients were separated based on smoking status. Clearly, smoking status may be a mediating factor in the effectiveness of collagen sponges on healing. It may be that smokers and non-smokers differ in terms of which treatment modality is best suited for quick and effective healing.

The effects of smoking on healing are well documented (Guo and Dipietro 2010). In a retrospective study of 916 flaps performed in the head and neck region resulted in a necrosis rate of 4.8% (Goldminz and Bennett 1991). When these patients were divided by smoking status, the results demonstrated that heavy smokers (1 or more pack/day) developed necrosis three times more frequently than non-smokers (Goldminz and Bennett 1991). In a population of breast cancer surgery, heavy smoking (≥15g per day) was significantly associated with post-operative infections with an odds ratio of 3.46 (Sorensen et al. 2002). In dental procedures, smoking is commonly associated with complications; one-article indicates a 50% complication rate for smokers who received onlay block grafts. In
addition, they state that smokers have higher rates of marginal bone loss around dental implants (Levin and Schwartz-Arad 2005). Other studies also report less favorable outcomes when treating periodontal patients for guided tissue regeneration (GTR) and surgical therapy (Preber and Bergstrom 1990; Tonetti et al. 1995)

The substances contained in tobacco smoke can interfere with wound healing in several ways. Tobacco can cause vasoconstriction, which limits the supply of nutrients to tissue and can decrease the white blood cell migration. Although Baab demonstrated that smoking does not impair gingival blood flow (Baab and Oberg 1987), other studies indicate that smoking generally decrease oxygen tension (Hunt et al. 1972; Jensen et al. 1991). In addition to decreasing oxygen tension, smoking has been shown to inhibit neutrophil and monocyte functions. This occurs by nicotine’s dose dependent action on the release of superoxides by neutrophils, thus limiting their bactericidal capabilities (Pabst et al. 1995). These factors can lead to increased tissue necrosis, infection, scarring and impaired/slowed healing time (Guo and Dipietro 2010).

Of the five patients, one claimed to be a smoker (< 10 cigarettes a day). In our study, the patient who was identified as a smoker contributed four subject sites (25% of total subject sites). When comparing this patient’s wound closure rate to the overall average of the non-smoking patients, they had considerably lower rates of wound margin migration 0.14mm vs. 0.46mm. This is consistent with literature that highlights the negative effects of smoking on healing and average epithelial
migration rate (Engler et al. 1966) (Siana et al. 1989; Ahn et al. 2008; Guo and Dipietro 2010). The slower wound closure rates in the smoker within the experimental group could be speculated to the fact that the collagen sponge may absorb the toxins from the cigarette and thus impede healing. The findings will need to be investigated in larger studies.

**Limitations and Future Directions**

A major limitation of our study was our sample size. During our enrollment, we only enrolled 5 patients with a total of 16 extraction sites. This has a major impact on the sample size and data interpretation. Our results are likely severely underpowered, and our risk of Type II error is extremely high. Future studies with larger sample sizes are imperative to make any concrete conclusions regarding the effects of collagen sponges on closure rate and post-extraction pain.

Although we attempted to keep the patients blind about the experimental and control sites, we are unsure if the patients were truly blinded. If a patient was aware of treatment and control sites, this potential knowledge of the experimental group could have influenced the results of the pain interpretation.

The measurements of wound closure are also subject to limitations. Our measurements of healing were based on the migration of the epithelial wound margin. In general, periodontal wound healing can be divided into four phases: 1) soft-tissue inflammation, 2) granulation, 3) intercellular matrix formation, and 4) remodeling (Ramseier et al. 2012). The best method to determine the stages of wound repair is to utilize histological analysis of the tissue in question. However, in
our experiment the examiners used their clinical judgment to locate the potential edges of the wound. This creates uncertainty of the measurable outcome; in essence, it is not possible to discern whether the recorded measurements were the true edges of the remodeled tissue. Although the measurement of the true location was a limiting factor of the study, our examiners did demonstrate reliability in their repeated measurements between one another. To some degree, this eliminates the absolute need to determine the true location of the wound margin. Another limiting factor during measurement was that the mesial-distal (MD) dimension of the extraction site made it difficult to position the probe for accurate measurement. This forces the examiners to interpret the recordings of the probe at an angle (fig. 2). However, since all the examiners were measuring under the same conditions it limits the confounding effects. During our patient selection, we attempted to enroll patients with similar sized dentition for the control and experimental groups. One hundred percent of the subjects had matching contra-lateral teeth that required extractions, 75% of the extractions were for facilitation of orthodontic treatment. As a result, we were able to limit the differences in the initial defect size between the control and experimental sites.

Although the effects of gender, defect size, smoking, and orthodontic appliances can variably affect the interpretation of wound closure rates and pain, our study was able to compensate for these confounding factors by subjecting each control and experimental site to the same conditions. We accomplished this through the split mouth design. However, further analysis showed that smoking may
mediate the material’s effectiveness, as such, future studies with the main goal to compare smokers and non-smokers would be beneficial as researchers and clinicians seek to determine which materials are best suited for smokers and non-smokers.

This project evaluated the short-term effects of collagen sponges in extraction sockets. Our data from pilot project indicated that there was a trend for the treatment group to heal at a faster rate than the control in non-smokers. Future long term studies with a larger population is necessary to explore the effect of the collagen sponge on wound closure and pain in both smokers and non-smokers. We also speculate that the use of a collagen sponge may have a potential effect on the ridge remodeling and that future studies should explore the effects of collagen sponges on ridge remodeling.
CHAPTER 5

CONCLUSION

Within the limitations of this in vivo study, the following conclusions can be made:

1. The use of collagen sponges in extraction sockets did not significantly ($p >0.05$) increase the rate of wound closure.

2. The patient’s postoperative pain did not significantly ($p >0.05$) decrease when utilizing the collagen sponge.
LITERATURE CITED


Ziccardi VB, Desjardins PJ, Daly-DeJoy E, Seng GF. Single-dose vicoprofen compared with acetaminophen with codeine and placebo in patients with
APPENDIX A

NUMERICAL RATING SCALE
NUMERICAL RATING SCALE

NRS - 1 represents the least amount of pain and 10 represents the greatest amount of pain. This is a modified version adapted from (Williamson and Hoggart 2005)
APPENDIX B

CONSENT FORMS
CONSENT FORM
A PILOT STUDY EVALUATING THE EFFECT OF COLLAGEN SPONGES ON HEALING AND PAIN FOLLOWING TOOTH EXTRACTION

Introduction

You are being asked to volunteer for a research study. This study is being conducted at The University of Missouri Kansas City School of Dentistry. The researcher in charge of this study is Dr. Keerthana Satheesh. While the study will be run by Dr. Satheesh, other qualified persons who work with her may act on her behalf.

The study team is asking you to take part in this research study because you have two or more teeth that need to be extracted. Research studies only include people who choose to take part. Please read this consent form carefully and take your time making your decision. The study doctor or staff will go over this consent form with you. Ask him/her to explain anything that you do not understand. Think about it and talk it over with your family and friends before you decide if you want to take part in this research study. This consent form explains what to expect the risks, discomforts, and benefits if any.
Background

We are seeking 20 patients who require two dental extractions, one each in opposite sides of the jaw. You must be physically healthy with no major medical conditions. We will be placing a material in one of the extraction sites. This material is commonly used in dental procedures.

Purpose

The purpose of this research study is to determine the beneficial effects of a dental product in an extraction site. The product comes from the tendon of a cow and is considered safe. This study may help determine if the product will help with discomfort and healing after the extraction.

You will be one of about 20 subjects in the study at The University of Missouri Kansas City, School of Dentistry.

Study Procedures and Treatments

If you decide to participate in this study, you will be asked for necessary registration information such as age, gender, race, and medical history. The dental extractions will be completed according to the surgical protocol; both teeth will be extracted on the same day. After the extractions, you will be given a journal to document your pain experience and medication use throughout the day. You will be required to document your pain level 3 times a day. A 3-day supply of pain pills will be given, and you will be asked to use the medication as needed. After the 3-day supply, if you need more medications you will have to buy them from the drug store. The time
required for this procedure is no different from that of a regular dental extraction, which can range from 30 minutes to two hours. After the extraction, you will be asked to return for three post-operative visits. These visits will be at 3 days, 7 days and 21 days following the tooth extraction. During these visits, we will take photographs and measure the area around the extraction site. Each visit after the extraction should only take about 20 minutes of your time.

If you agree to take part in this study, you will be involved in this study for 3 weeks and will only be required to show up 3 times after the extraction visit for a total of 4 visits.

**Photographs:**

Photographs will be taken of the extraction area only. The photographs will only show the area inside the mouth. The face will not be seen.

**The following study visits and procedures will occur:**

Following enrollment into the study, on the first visit, you will have your teeth extracted. Before the extraction, you will rinse with a mouthwash that will decrease the amount of bacteria in your mouth. After the teeth have been extracted, we will place the dental product in one of the extracted sites and stitch (suture) it in place. After that has been completed, we will take pictures of the treatment. The other extraction site that does not get the dental product is considered the control. The control side will be determined by a coin toss. Only one extraction site will be treated
with the dental product. The side that is not treated by the product will be allowed to heal on its own. Allowing sockets to heal on their own is a common protocol.

There will be a total of 3 visits after the treatment. All these visits will be located at the Graduate Periodontics clinic at the University Of Missouri Kansas City, School Of Dentistry. At each visit, a picture will be taken of the previously treated sites to document healing.

**Example of visits (following enrollment)**

**Visit 1-** Extraction of teeth and placement of material in one site and nothing on the other. Stitches will be placed on both. We will review the instructions and the use of the journal.

**Visit 2-** This visit will occur 3 days after the extractions. We will photograph the two sites with a measuring tool in place. We will review your journal.

**Visit 3-** 1 week after the extraction, we will photograph the two sites with a measuring tool in place. We will review your journal.

**Visit 4-** 3 weeks after the extraction, we will photograph the two sites with a measuring tool in place. We will review your journal.

If you withdraw early from the study, you will be asked to complete an end of study visit.
**Possible Risks or Side Effects of Taking Part in this study**

The dental product selected for this study has been approved by the FDA and has no documented risks. Procedures for extracting teeth have been long established; the risks involved are the same as with any other regular extraction. This includes jaw fracture, soreness of the jaw, bleeding, post-operative pain, swelling, instruments hitting surrounding teeth, a hole connecting your sinus cavity and bone loss. This will be outlined in detail in the School of Dentistry surgical consent form that you will be required to sign.

The known risks of using the collagen product include the following:

- Having an allergic reaction,
- The collagen material not sticking to the tissue, and
- Fluid buildup in the tissue where the product is used (only one reported case).

Since this is a collagen product, any adverse reactions that have happened with other types of collagen material might happen with this product. Although these are potential reactions to the product, it is extremely rare and uncommon.

**Possible Benefits for Taking Part in this Study**

The potential benefits of participating in this study may include increased healing and decreased post-operative pain. In addition, you will be compensated for your time and closely followed after the procedure.
Costs for Taking Part in this Study
You will pay for two extractions, $60.00 per tooth. You will not have to pay for the
dental product (approximately $40.00) or any of the post-operative visits.
You will be responsible for any dental visit as usual except for those directly related
to the research study.

Payment for Taking Part in this Study
To compensate you for your time and transportation expenses you will be paid $10
for visit 2 (day 3) and visit 3 (day 7) of the study that you complete. For the visit
4(day 21), you will receive $30. You will be paid a total of $50 for completing all four
visits of the study.

Alternatives to Study Participation
Alternatives to this study are to not participate.

Confidentiality and Access to your Records
The results of this research may be published or presented for scientific purposes.
You will not be named in any reports of the results. Your study or applicable medical
records that have your identity in them may be shown to the Institutional Review
Board (IRB) (a committee that reviews and approves research studies), The Food
and Drug Administration or other governing agencies. This is to prove which study
procedures you completed and to check the data reported about you. They may also
review your medical records for any treatment you received before you agreed to
take part in this study. This is to confirm your medical history and that you meet the requirements to be in this study. The study team will keep all information about you confidential as required by law, but complete confidentiality cannot be guaranteed. If you leave the study or are removed from the study, the study data collected before you left may still be used along with other data collected as part of the study. For purposes of follow-up studies and if any unexpected events happen, subject identification will be filed in a locked file cabinet in room #3101 at the School of Dentistry, under appropriate security and with access limited to the study research personnel only.

If you sign this consent form, you are allowing the study team and these other agencies to see your medical records.

**In Case of Injury**

Truman Medical Center (TMC) will provide medical attention to you in the event of any medical emergency while present at TMC from participation in this research, whatever the cause at the usual charge and you will have the benefit of the coverage of any existing health insurance you own.

Participation in this research study does not take the place of routine dental examinations or clinic visits to your personal dentist. If you believe, you have been injured as a result of participating in this study you are encouraged to contact the study investigator Dr. Keerthana Satheesh at 816-235-2075.
The University of Missouri-Kansas City appreciates people who help it gain knowledge by being in research studies. It is not the University’s policy to pay for or provide medical treatment for persons who participate in studies. If you think you have been harmed because you were in this study, please call the researcher, Dr. Keerthana Satheesh at 816-235-2075.

**Contacts for Questions about the Study**

You should contact the IRB Administrator of UMKC’s Adult Health Sciences Institutional Review Board at 816-235-5927 if you have any questions, concerns or complaints about your rights as a research subject. You may call the researcher Dr. Satheesh at 816-235-2075 if you have any questions about this study.

**Voluntary Participation**

Taking part in this research study is voluntary. If you choose to be in the study, you are free to stop participating at any time and for any reason. If you choose not to be in the study or decide to stop participating, your decision will not affect any care or benefits you are entitled to. The researchers, doctors or sponsors may stop the study or take you out of the study at any time:

- if they decide that it is in your best interest to do so,

- if you experience a study-related injury,

- if you need additional or different medication/treatment,

- if you no longer meet the study criteria, or

- if you do not comply with the study plan.
They may also remove you from the study for other administrative or medical reasons. You will be told of any important findings developed during the course of this research.

You have read this Consent Form or it has been read to you. You have been told why this research is being done and what will happen if you take part in the study, including the risks and benefits. You have had the chance to ask questions, and you may ask questions at any time in the future by calling Dr. Satheesh at 816-235-2075 or Dr. Norouzinia at 816-235-2147. By signing this consent form, you volunteer and consent to take part in this research study. Study staff will give you a copy of this consent form.

__________________________________  ________________
Signature (Volunteer Subject)               Date

__________________________________
Printed Name (Volunteer Subject)

__________________________________  ________________
Signature (Authorized Consenting Party)    Date

__________________________________
Printed Name (Authorized Consenting Party)
Relationship of Authorized Consenting Party to Subject

Signature of Person Obtaining Consent               Date

Printed Name of Person Obtaining Consent
APPENDIX C

POST-OPERATIVE INSTRUCTIONS
POST-OPERATIVE INSTRUCTIONS

Immediately following extraction:

- Keep the gauze over the surgical area with pressure applied by biting down until bleeding stops.
- Take your prescribed pain medication as needed. Do not exceed total recommended dosage i.e. Ibuprofen 600 mg every 6 hours, do not exceed 3200mg in a 24 hour time period.
- If you continue to experience pain and feel like you need something stronger for pain please call the investigator.
- On the day of the extraction, restrict your activities. Resume normal activity when you feel comfortable.
- Avoid vigorous mouth rinsing or touching the affected area following the extraction. Do not rinse your mouth the first post-operative day or while there is bleeding. Rinse with the prescribed mouth rinse after the first day.

(1/2 capful in the morning and 1/2 capful in the afternoon)

- Sleep with head slightly elevated.
- Place ice pack for twenty minutes when you have returned home and before you go to bed.
- Avoid eating foods that are rigid, abrasive, and hot in temperature, examples: Doritos, chips, hot soup, etc.
• Do not touch or cut the sutures. Suture will be removed at the postoperative appointment.

**Documentation for journal:**

• In your journal record your pain each day.

• The scale on the left corresponds to the tooth on the left and the scale on the right corresponds to the tooth on the right. MAKE SURE YOU DOCUMENT THE PROPER SIDE.

• The #10 on the scale represents the worst pain you can feel and the #1 is the least pain.

• Pick a number that corresponds to your level of pain at that moment. This will be recorded 3 times each day: 1) When you wake up; 2) in the afternoon after lunch; and 3) before bedtime.

• If you require the use of Ibuprofen for pain, please document when the medication was taken and indicate which side caused you to take the medication. If both sides are causing pain try to indicate which side hurts more, if you are unable to tell write N/A. This will be documented on the back of the journal.
NAME: Bahman Norouzinia

DATE AND PLACE OF BIRTH: March 24, 1985, Tehran, Iran

MARITAL STATUS: Single

EDUCATION:
5/31/02 Diploma James Martin High School
5/31/06 B.S. Biology University of Texas at Arlington
5/31/11 D.D.S. University of Texas Health Science Center at San Antonio College of Dentistry

PROFESSIONAL ORGANIZATIONS:
2007-2008 Member of the American Student Dental Association (ASDA)
2007-2009 Member of Xi Psi Phi Dental Fraternity
2007-2012 Member of the Christian Medical and Dental Association

HONORS:
2006 Magna Cum Laude, University of Texas at Arlington
2002-2006 Dean’s List, University of Texas at Arlington
2002-2003 Freshman’s Honor List, University of Texas at Arlington