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Comparison of Efficacy of *Serratiopeptidase* and *Escin* after Impacted Mandibular Third Molar Surgery: A Randomized Controlled Clinical Trial

A Proposal Submitted by

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To

The Council of Postgraduate Studies and Scientific Research, in Partial Fulfillment of the Requirements for the Master program of Dental Sciences in Oral Surgery and Dental Implantology

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List of Abbreviations

CBCT	Cone-Beam Computed Tomography
IAC	Inferior Alveolar Canal
MMOA	Maximum Mouth Opening Ability
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
USTY	University of Science and Technology, Yemen
VAS	Visual Analogue Scale

Chapter 1:

Introduction

1.1. Background

The surgical removal of impacted third molars, commonly known as wisdom teeth, remains a frequent procedure in oral and maxillofacial surgery. While the procedure itself is routine, it often leads to undesirable post-operative complications such as pain, trismus (limited jaw opening), and facial swelling (Al-Khateeb & Nusair, 2008; Brković et al., 2017). These complications arise from the natural inflammatory response triggered by the surgical trauma.

Traditionally, the management of these complications has relied on pharmacological interventions, primarily corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) (Kaplan & Eroğlu, 2016). These medications offer potent anti-inflammatory and analgesic properties, effectively reducing pain and swelling. However, their use is often associated with undesirable side effects, including gastrointestinal bleeding, renal dysfunction, and blood dyscrasias, raising concerns regarding their long-term safety (Piecuch, 2012). Recognizing these limitations, researchers have explored alternative therapies with potentially fewer side effects. Among these promising alternatives are therapeutic enzymes and phytotherapeutic drugs derived from natural sources.

Serratiopeptidase, a proteolytic enzyme, has emerged as a potential candidate for managing post-surgical inflammation. Studies have shown its effectiveness in reducing inflammation around teeth and dental implants, suggesting its potential benefit after third molar extraction (Sannino et al., 2013; Villafuerte-Nuñez et al., 2013). However, existing research in this area remains limited, particularly regarding its efficacy in managing post-operative complications following third molar teeth removal.

Similarly, phytotherapeutic drugs offer a promising avenue for post-surgical pain and swelling management. These natural extracts have demonstrated their effectiveness

in treating various inflammatory conditions and postsurgical complications (Olmedo-Gaya et al., 2016; Pavan et al., 2012). Notably, studies have shown their ability to reduce pain and discomfort after third molar surgery, highlighting their potential as safe and effective therapeutic options (Isola et al., 2019). One such phytotherapeutic drug, escin, derived from horse chestnut, has exhibited potent anti-inflammatory activity, suggesting its potential benefit in reducing post-surgical inflammation and swelling (Wang et al., 2009).

Despite the promising results observed with both serratiopeptidase and escin, significant research gaps remain regarding their specific efficacy in managing post-operative complications following impacted third molar surgery. Existing studies are often limited in scope and methodology, necessitating further investigation to fully understand their potential benefits. Therefore, this study aims to address these research gaps and provide definitive answers to the study main questions.

1.2.Statement of the Problem

Impacted third molar extraction is the most commonplace surgical procedure in oral surgery (Brković et al., 2017). This surgical procedure results in the most common detected post-operative complications which are trismus, swelling, and pain due to the inflammatory process (Bataineh & Batarseh, 2017). To treat post-operative complications, many strategies have been developed to decrease clinical occurrence after surgery through a pharmacological approach by inhibiting inflammatory processes of acute inflammation. Out of these, corticosteroids and NSAIDs have shown immunosuppressive, anti-inflammatory, and analgesic effects (Isola et al., 2016; Kaplan & Eroğlu, 2016). Though, the use of corticosteroids or NSAIDs has been related to some side

effects like gastrointestinal bleeding, renal function disturbance, a reduction in platelet function, shortness of breath, and profound hypotension (Piecuch, 2012).

Therefore, researchers have been working on alternative therapies including the use of therapeutic enzymes and phytotherapeutic drugs composed of herbal extracts. A proteolytic enzyme, serratiopeptidase, has shown positive results in inflammatory disorders around teeth and dental implants (Sanninol et al., 2013; Villafuerte-Nuñez et al., 2013). So far, published studies assessing the efficacy of serratiopeptidase after third molar extraction are minor with inadequate methodological quality (Al-Khateeb & Nusair, 2008; Chopra et al., 2009; Mouneshkumar et al., 2015).

In contrast, for many years, many phytotherapeutic drugs have been widely used for the treatment of inflammatory diseases and postsurgical conditions (Olmedo-Gaya et al., 2016; Pavan et al., 2012). There were favorable effects in the inflammatory parameters, when the phytotherapeutic drugs were used as a post-operative therapy of third molar surgery, The phytotherapeutic drug as a mixture of herbal extract with anti-inflammatory activity was shown to be safe and simple in the control of pain and control postsurgical discomfort after surgical removal of the third molar. Further studies are needed to understand better the role and potential benefits of phytotherapeutic drugs in the therapy after the removal impacted third molar (Isola et al., 2019). Escin is a natural molecule with a major active component of Aesculus hippocastanum. It is a natural mixture of triterpene saponins and has shown clinically considerable anti-inflammatory activity postoperatively and in traumatic injuries (Wang et al., 2009).

Based on the research gaps recommend by (Al-Khateeb & Nusair, 2008; Chopra et al., 2009; Mouneshkumar et al., 2015) to assess the efficacy of serratiopeptidase after third molar extraction and (Isola et al., 2019) to understand potential benefits of escin after the removal impacted third molar, the study aims at finding solid answers to the following main questions:

1. Does serratiopeptidase, when used in addition to conventional drugs, offer greater efficacy in reducing post-operative pain, trismus, and facial swelling compared to conventional drugs alone following impacted third molar surgery?
2. Does escin, when used in addition to conventional drugs, offer greater efficacy in reducing post-operative pain, trismus, and facial swelling compared to conventional drugs alone following impacted third molar surgery?
3. When both serratiopeptidase and escin are used in addition to conventional drugs following impacted third molar surgery, which one demonstrates superior efficacy in reducing post-operative pain, trismus, and facial swelling?

1.3.Justification of the study

There is a high prevalence rate of impacted lower third molars with many complications. To the best of the researcher's knowledge, no clinical study has been conducted aiming to compare the efficacy of serratiopeptidase and escin after impacted third molar surgery in order to minimize in the most common detected post-operative complications.

1.4.Objectives of the study

Based on the above introduction and study question, the objectives can be classified into general and specific as follows:

General objective

The overall purpose of this study is to compare the efficacy of serratiopeptidase and escin in the reduction of post-operative complications (i.e., pain, trismus, and facial

swelling) following impacted third molar surgery, when both used in addition to conventional drugs.

Specific objective

1. Evaluate the efficacy of serratiopeptidase, when used in addition to conventional drugs, in reducing post-operative pain, trismus, and facial swelling following impacted third molar surgery.
2. Evaluate the efficacy of escin, when used in addition to conventional drugs, in reducing post-operative pain, trismus, and facial swelling following impacted third molar surgery.

1.5.Study Hypotheses

Based on the study main problem, objectives, and literature review, three main hypotheses are constructed in order to test the relationship between the study variables. These hypotheses are listed in this section as follows:

1. There is a statistically significant difference in serratiopeptidase, when used in addition to conventional drugs, in reducing post-operative pain, trismus, and facial swelling compared to conventional drugs alone following impacted third molar surgery.
2. There is a statistically significant difference in escin, when used in addition to conventional drugs, in reducing post-operative pain, trismus, and facial swelling compared to conventional drugs alone following impacted third molar surgery.
3. There is a statistically significant difference in serratiopeptidase in reducing post-operative pain, trismus, and facial swelling compared to escin, when

both used in addition to conventional drugs, following impacted third molar surgery.

Chapter 2:

Literature Review

2.1.Impacted Third Molar

The third molars, commonly known as wisdom teeth, often lead to complications during eruption, presenting a frequent concern in oral surgery (Wray et al., 2003). (Lytle, 1979) defines an impacted tooth as "*a tooth that has failed to erupt into its normal functional position beyond the time usually expected for such appearance. Eruption may have been prevented by adjacent hard or soft tissue including tooth, bone, or dense soft tissue*". Among impacted teeth, mandibular third molars are the most common, followed by maxillary third molars and maxillary canines. Most unerupted teeth are extracted due to pain or infection, but other reasons include involvement in pathologies like cysts or tumors, causing resorption of adjacent teeth, or interfering with surgical procedures (Undrell Moore, 2011).

2.1.1. Etiology of Impaction

Several theories attempt to explain the cause of impacted wisdom teeth, as outlined by (Varghese, 2021). The most widely accepted include:

1. Disparity in tooth size and arch length: The jaw size may be insufficient to accommodate the wisdom teeth, leading to impaction.
2. Differential root growth: The uneven growth of mesial and distal roots can hinder eruption.
3. Delayed dental development: The wisdom teeth's development may lag behind skeletal growth, preventing proper eruption.
4. Decreased molar extractions: Early dental interventions and increased awareness have led to fewer extractions of permanent molars, resulting in less space for wisdom teeth.

2.1.2. Classification of Impaction

The core classification system of impacted third molars is the foundation for understanding their diverse clinical presentations and facilitating successful transalveolar extraction. This system helps categorize impacted teeth based on several key factors, outlined by (Bhargava, 2022):

1. Winter's classification (developed in 1926) focuses on the angulation of the impacted third molar relative to the long axis of the adjacent second molar ((Yilmaz et al., 2016).
2. The Pell and Gregory classification system, proposed in 1933, assesses the position of impacted third molars based on two key factors: depth and the availability of space (Jaroń & Trybek, 2021).
3. Rood's criteria, proposed by Rood and Shehab in 1990, focuses on radiographic features indicating a close relationship between the impacted third molar and the mandibular canal (Rood & Shehab, 1990).
4. (Maglione et al., 2015) proposed a classification system specifically designed for evaluating impacted third molars using cone-beam computed tomography (CBCT) images.

2.1.3. Indications and Contraindications for Removal of Impaction

Several indications justify the extraction of wisdom teeth, as outlined by (Wray et al., 2003) in Table 2-1, including pericoronitis, infection, cystic change, etc. While extraction is the common course of treatment, there are situations where it may be contraindicated, as outlined in Table 2-2, such as high risk of damaging important structures, poor systemic health, or possibility of non-surgical treatment (Chiapasco et al., 2018).

Table 2-1 Indications for Removal of Impacted Third Molars.

Indications		Description
Infection	Pericoronitis	If the first episode is very acute or there has been more than one episode.
	Untreatable caries, pulpal or periapical pathology	The patient is unable to clean the distal aspect of the second molar or the area around the wisdom tooth, which is often partially erupted. This leads to the accumulation of food debris and plaque and then caries of the adjacent tooth surfaces.
	Periodontal disease	As a result of the unsatisfactory relationship between the second and third molars, the area is prone to periodontal disease, which may compromise the second molar.
Cystic change		When third molars are unerupted they may be the source of a dentigerous cyst, which can enlarge considerably before giving rise to symptoms.
External or internal resorption		External resorption of the second molar due to pressure from the unerupted third molar. Internal resorption within the wisdom tooth
Wisdom tooth in tumour resection		If an impacted wisdom tooth is associated with a tumour at the angle of the mandible, or is within the tumour resection margins.
Transplantation		When a patient presents with a heavily restored or carious first molar tooth and a partially erupted third molar tooth it is possible to transplant the third molar into the socket of the first molar.
Fractured mandible		If a fracture of the mandible through the angle occurs, an opportunity may arise to remove the third molar when surgical access is being made to treat the fracture itself.
Atrophic mandible		Third molar in an already atrophic mandible might be a potential site for fracture
Denture or implant design		To facilitate denture design or the accurate placement of implants.
Access to dental care		Where patients are in a situation where they do not have easy access to dental care
Medical condition		Removal of third molars following radiotherapy increases the likelihood of the development of osteoradionecrosis. Prior to cardiac surgery is another example.
Orthodontic considerations		To prevent or reduce imbrication of the incisor teeth.
Orthognathic surgery or reconstructive surgery		When orthognathic surgery is being planned, particularly with procedures such as sagittal split osteotomy.

Indications	Description
Age of patient	For young fit patients and not leaving them until an older age when the bone is denser and more difficult to manage, and when the patient may have medical problems related to older age group.

Table 2-2 Contraindications to Extraction of Impacted Third Molars.

Contraindication	Description
High risk of damaging important anatomic structures	A CT scan is mandatory to check the relationships between the impacted tooth and the involved anatomic structures
Compromised systemic conditions and age of the patient	It can be removed for patients with a partially compromised systemic condition under the following notes: 1. close cooperation with the specialist in charge of the patient 2. perform surgical intervention in a protected environment (e.g., hospital), 3. the possibility to monitor the patient's vital signs. 4. assistance from an anaesthetist/intensive care doctor. In elderly patients, this type of surgery can be more invasive due to the higher risk of tooth ankylosis.
Possibility of surgical exposure and orthodontic treatment, or autotransplantation	In these cases, it's better to align the impacted teeth by the orthodontic treatment or autotransplantation rather than removal.
Poor patient compliance	When the patient is uncooperative

2.1.4. Techniques for the Removal of Impacted Third Molars

The typical operative plan for impacted third molar extraction entails five main stages: 1) Incision 2) Bone Removal 3) Tooth Sectioning 4) Delivery 5) Wound Closure. However, some additional methods are also mentioned, including sagittal split osteotomy, buccal corticotomy technique, lingual split bone technique, lateral trepanation technique, partial odontectomy/coronectomy, and removal after orthodontic extrusion (Varghese, 2021)

2.1.5. Complications of the Removal of Impacted Third Molars

Possible complications of third molar removal include nerve numbness (paresthesia), dry socket (alveolar osteitis), infections, bleeding, jaw fracture, bone infection (osteomyelitis), damage to neighboring teeth, exposed fat pad in the cheek, opening between the mouth and sinus cavity (oral-antral communication), displaced teeth, inhaled objects (aspiration), gum tissue damage (periodontal defects), and jaw joint problems (temporomandibular joint injury). The four most common complications are nerve numbness, dry socket, infections, and bleeding (Bouloux et al., 2007).

While pain, swelling, and trismus are expected following surgery, poor surgical technique can exacerbate these issues. Pain management relies on analgesics administered before anesthesia wears off. Persistent pain indicates potential infection or dry socket requiring follow-up. Transdermal patches have shown effectiveness for post-extraction pain (Bhargava et al., 2019). Trismus may arise from injury to the medial pterygoid muscle or inflammation/hematoma at the extraction site (Fragiskos, 2007). Proper patient selection and surgical skill can minimize risks.

2.2. Post-operative Treatment following Third Molar Surgery.

Following third molar surgery, a course of conventional medication is typically prescribed to manage pain, swelling, and infection. Pain management commonly involves NSAIDs like ibuprofen or naproxen (Bhargava et al., 2019), while antibiotics may be employed to prevent or treat infection (Malamed, 2019). Additionally, corticosteroids may be used to combat inflammation and reduce swelling (Undrell Moore, 2011). To ensure optimal healing and minimize discomfort, adhering to the prescribed medication regimen and following post-operative instructions are crucial (Wayland, 2024).

Emerging research suggests potential benefits for both enzymes and phytotherapeutic drugs in managing post-surgical pain and swelling. Serratiopeptidase, a proteolytic enzyme, has shown promise in reducing inflammation around teeth and implants, potentially offering similar benefits after third molar extraction (Sannino et al., 2013; Villafuerte-Nuñez et al., 2013). Escin, a phytotherapeutic drug derived from horse chestnut, exhibits potent anti-inflammatory properties, suggesting its potential in reducing post-surgical inflammation and swelling (Wang et al., 2009). Figure 2-6 summarizes and compares between both medicines as follows:

Feature	Serratiopeptidase	Escin
Chemical Structure	Zinc-containing protein (metalloprotease)	Mixture of triterpenic glycosides
Source	Enterobacterium Serratia	Horse chestnut seeds
Pharmacokinetics	Limited absorption through intestines, distributed to sites of inflammation	High concentrations in skin and muscle, minimal internal distribution
Pharmacodynamics	Anti-inflammatory, analgesic, fibrinolytic, anti-biofilm, wound healing	Anti-edematous, anti-inflammatory, venotonic
Administration	Oral tablets	Oral tablets, topical gels/creams
Dosage	10-60 mg/day (2000 units/mg)	20 mg/day (oral), 1-2 applications/day (topical)
Complications	Rare adverse reactions like Stevens-Johnson syndrome, esophageal ulcers	Hepatic injury, toxic nephropathy
Contraindications	Pregnancy, breastfeeding, hemophilia, liver/kidney dysfunction, concurrent use with antiplatelet drugs/anticoagulants/natural supplements	Pregnancy, breastfeeding, renal/hepatic impairment
Therapeutic Applications	Oral and maxillofacial surgery (post-operative pain/swelling), inflammation, infections, major surgeries, traumatic injuries	Chronic venous insufficiency, hemorrhoids, post-operative edema, cerebral/intracranial edema, gynecology, periodontitis

Figure 2-1 Serratiopeptidase vs. Escin: A Comparative Table.

2.3.Split-mouth Randomized Controlled Trials

Dental clinical trials offer two options for randomizing treatments: over individuals (mouth-level) or over sites within the mouth (site-level). The parallel-group design, where the same treatment is applied throughout the entire mouth, is the simplest and most commonly used approach. On the other hand, the split-mouth design involves random assignment of treatments to specific sites within the mouth. This design utilizes each person as their own control, allowing for more precise treatment comparisons

(Lesaffre et al., 2009). The split-mouth design was introduced by (Ramfjord et al., 1968) to compare the effectiveness of different periodontal therapies within each subject's mouth. The design divides the mouth into two halves, randomly assigning different treatments to each half.

The split-mouth design compares treatments within each patient, avoiding bias that may arise when comparing separate cases and controls. It eliminates inter-subject variability and produces reliable results (Kazancioglu et al., 2014; Lesaffre et al., 2007). Compared to between-patient designs, the split-mouth design offers increased efficiency, requiring fewer participants and resources while achieving similar results. However, it also presents the potential for carry-across effects, where the treatment on one side of the mouth influences the response on the other side (Hujoel & Loesche, 1990; Varma & Chiilton, 1974). To estimate treatment effects in a split-mouth design, researchers make assumptions about carry-over effects. Common assumptions include no carry-over effect, complete carry-over effect, and partial carry-over effect. These assumptions cannot be tested within the study itself and rely on prior knowledge (Hujoel & DeRouen, 1992).

When choosing a split-mouth design, researchers should consider bias, recruitment challenges, efficiency, and statistical analysis. Careful evaluation of potential carry-over effects is crucial to avoid bias. Finding suitable patients with symmetrical dental conditions can be difficult, and statistical analysis requires more complex methods compared to whole-mouth designs (Hujoel, 1998). Controlling carry-over effects in split-mouth studies is challenging. Washout periods of at least three weeks between treatment applications can help mitigate carry-over effects by allowing the body to eliminate residual effects of previous treatments (Gozali et al., 2017). Understanding the advantages, limitations, statistical considerations, and implications of the split-mouth design is essential for researchers in both the statistical and clinical fields. This knowledge

enables effective utilization of the design while acknowledging its potential drawbacks (Lesaffre et al., 2009).

Chapter 3:

Material and Methods

3.1. Study Design

This clinical trial will utilize a split-mouth design, randomly assigning two different treatments to each half of the patient's mouth. From this randomized study which is characterized by a triple-blind study, the procedures are going to be performed by qualified and experienced professional. However, the operator will have no access to data evaluated. The evaluator will have access to all responses of the symptoms of patients and will not know the treatment that is going to be selected, while the patient is unaware of which treatment or intervention is being applied to each side of their mouth. This stringent blinding approach minimizes potential biases and significantly enhances the scientific validity of the study.

Patients will be assigned into two groups and each patient acted as their own control using the split-mouth technique. One impacted third molar will be removed from one side and will receive conventional drugs while the other side will be removed after 3 weeks (wash-out period) and receive additional treatment beside the conventional drugs (i.e., either enzyme or herbal). The two groups will be classified as follows:

- The first group will receive conventional drugs with 10mg oral serratiopeptidase at immediate post-operative time and three times a day for post-operative five days on the first surgical visit and on the second surgical visit (after 3 weeks) conventional drugs will be given only or vice versa.
- The second group will receive conventional drugs with 20mg oral escin at immediate post-operative time and three times a day for post-operative five days on the first surgical visit and on the second surgical visit (after 3 weeks) conventional drugs will be given only or vice versa.

The conventional drugs, it will be administered to patients in the two groups, includes: Amoxicillin 500mg Cap b.i.d., Metronidazole 500mg Tab t.i.d., Diclofenac sodium 50mg Tab b.i.d.

3.2.Study Population

The study population will include patients who will visit the dental clinics in the College of Dentistry, University of Science and Technology, Yemen (USTY) for impacted mandibular third molars extraction during 2024.

3.3.Sample Size

The sample size is the number of participants planned to be included in the trial, usually determined using a statistical power calculation (Zanatta et al., 2017). This study determined the sample size using a power calculation based on previous research by (Costa et al., 2015). Their study found that preemptive use of etoricoxib 120mg significantly reduced the need for rescue analgesic medication compared to a placebo (1.6 ± 1.3 vs 4.0 ± 2.5). To achieve a power of 80% and a confidence interval of 95%. The study will need to evaluate 11 surgical sites per sub-group (http://www.openepi.com/SampleSize/SSMean.htm). To account for a potential 20% drop-out rate, a total of 14 sites per sub-group will be recruited. This will result in a total sample size of 56 dental units (2 teeth per patient) from 28 patients. The following Table 3-1 illustrates the study sample size and the planned treatment.

Table 3-1 : Sample Size and Study Treatment.

Groups	I		II		Total
Patients	14		14		**28**
Sub-groups	Control 1	Study 1	Control 2	Study 2	**4**
Sample size	14	14	14	14	**56**
Conventional Treatment	Amoxicillin 500mg Cap b.i.d Metronidazole 500mg Tab t.i.d Diclofenac sodium 50mg Tab b.i.d				**N/A**
Study Treatment	N/A	Serratiopeptidase 10mg t.id	N/A	Escin 20mg t.id	**N/A**

3.4.Sample Selection

Patients who will undergo to surgical removal of the impacted third molar will be assessed for their eligibility to participate according to the following inclusion and exclusion criteria:

Inclusion criteria:

- Medically fit patients.
- The presence of two asymptomatic mandibular third molar indicated for surgical extraction.
- Absence of pericoronitis or signs of inflammation during the last 30 days

Exclusion criteria:

- Patient administered other drugs such as NSAIDS and steroids.
- Patient has allergy to the drugs used in this study.
- Pregnant patient or a patient with lactation.
- Immunocompromised patients with diabetic or hypertension (from patient's history).
- Patients with irradiated maxillofacial region.
- Intellectually disabled patients and patients unable to come for follow up visits.
- Patients with acute and subacute pericoronitis

3.5.Randomization

This clinical trial will utilize simple randomization based on the technique described by (Oliveira et al., 2021). This method involves drawing envelopes to determine the following:

- Surgical site: Test or control side
- Tooth: Right third molar ("A") or left third molar ("B")
- Surgery order: First or second session

The following steps of randomization will be followed:

1. Draw the tooth: An envelope is drawn to determine which third molar will be extracted first (right or left).
2. Draw the intervention: A second envelope is drawn to determine whether the selected tooth will receive the test intervention ("X-1") or no intervention ("X-2").
3. Draw the surgery order: A final envelope is drawn to determine whether the selected tooth will be extracted in the first or second surgery session.

3.6. Pre-operative and Post-operative Assessment

Prior to surgical removal of impacted third molar, preoperative variables (i.e., pain, trismus, and facial swelling) will be taken for each patient and recorded in the data collection sheet. Furthermore, the same post-operative variables (preoperative variables) will be taken immediately after the procedure, 2nd day, 3rd day and 5th day after the operation. Both pre-operative and post-operative variables will be done by the same measurements.

3.6.1. Assessment of Pain

Measurements of this outcome will consider pain intensity based on Figure 3-1. Preoperative and postoperative pain intensity will be assessed using a standardized 10-centimeter visual analogue scale (VAS), ranging from 0 (no pain) to 10 (worst possible pain) (Sirintawat et al., 2017). Prior to surgery, patients will receive thorough instructions on using the VAS to accurately self-report their pain. Following the procedure, they will record their pain scores on a standardized form and return it to the researcher on the day of suture removal, allowing for continuous monitoring and evaluation of pain management effectiveness (Costa et al., 2015).

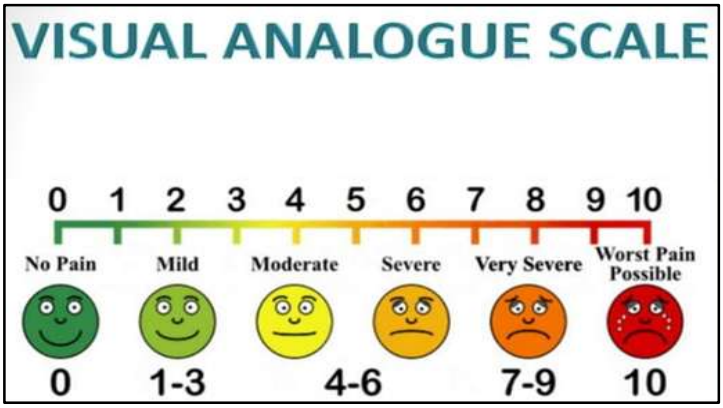

Figure 3-1 Pain Intensity Measurement.

3.6.2. Assessment of Mouth Opening (Trismus)

Measurements of this outcome will be via comparing the difference in maximum mouth opening ability (MMOA) before and after surgery (Figure 3-2). This will be achieved by using a calibrated ruler to measure the distance between the upper and lower central incisors in millimeters, both preoperatively (baseline) and at defined post-operative time points. This approach allows for a quantifiable assessment of trismus development and recovery following the intervention (Sreesha et al., 2020).

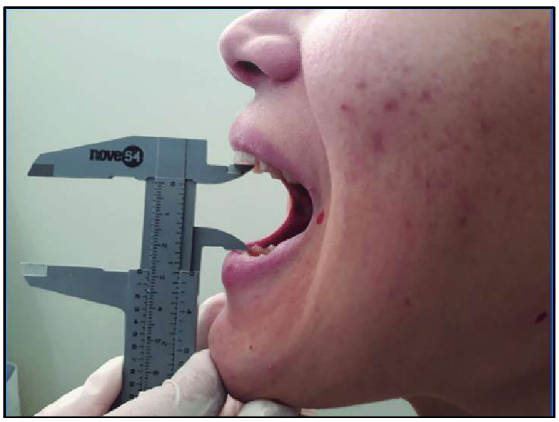

Figure 3-2 Trismus Measurement - MMOA.

3.6.3. Assessment of Facial Swelling (Edema)

This outcome will be evaluated through using the method described by (Schultze-Mosgau et al., 1995) to quantify facial swelling pre- and post-operatively. Measurements will be taken with a flexible scale in the closed mouth position by marking five fixed points and three surgical base lines connecting the said fixed points as follows:

- 5 fixed points (F1 – tragus of ear, F2 – angle of mandible, F3 – soft tissue pogonion, F4 – Corner of mouth, F5 – lateral canthus of eye)
- 3 surgical base lines (S1 – from tragus of ear to corner of mouth, S2 – from tragus of ear to soft tissue pogonion, S3 – from lateral canthus of eye to angle of mandible).

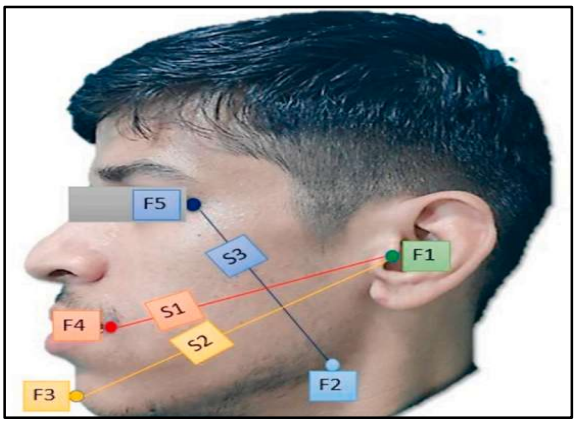

Figure 3-3 Swelling Measurement.

3.7.Surgical Procedures

To minimize variability and bias, all surgical extractions will be performed by the same oral surgeon utilizing a uniform technique (Isola et al., 2019). Each patient will receive similar operative procedures under identical conditions, including administration of local anesthetic consisting of inferior alveolar, lingual, and long buccal nerve blocks. Additionally, the same surgical procedure will be adopted for all groups. Access to the third molar will be achieved from the buccal aspect. A mucoperiosteal flap will be raised, and bone removal with a round bur in a straight handpiece under continuous irrigation with a sterile saline solution and/or tooth sectioning will be performed. After tooth extraction, the alveolus will be inspected, curetted for granulation tissue removal, and irrigated with a sterile saline solution. The surgical wound will be closed using a 4–0 reabsorbable suture (Coated VICRYL). This meticulous approach minimizes intraoperative trauma and ensures consistency across all groups.

Post-operatively, patients will receive their assigned medications and receive thorough instructions regarding dietary restrictions (liquid and cold diet for 24 hours), oral hygiene practices, and avoidance of mouthwashes to prevent bleeding. They will be informed about potential complications and instructed to contact the surgeon if any issues arise. Additionally, they will be requested to report any physical symptoms experienced during the study period.

3.8. Ethical Consideration

The ethical approval will be obtained from the USTY Medical Research Ethics Committee. The purpose and methodology of the study will be explained to all the participants. Hence, a participant information sheet (Appendix B) will be given to all participants and a written informed consent form (Appendix C) will be obtained from them with the tenets of the revised Declaration of Helsinki 1975.

3.9. Statistical Method

Quantitative data (pain, trismus, and facial swelling) will be expressed as means and standard deviations and compared using the paired t test (parametric) or Wilcoxon test (nonparametric). The Shapiro–Wilk test will be used to verify the normality of the data. A difference of $P < .05$ will be considered statistically significant. The data analysis will be performed using SPSS V.25 (SPSS, JASP).

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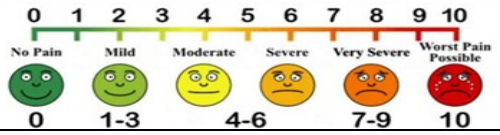
Appendix A: Case Sheet

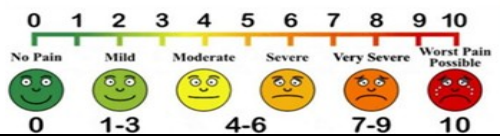
PERSONAL DETAILS	
Case no.	
Name of patient	
Age	
Sex	
Occupation	
Contact no.	
Address	

MEDICAL STATUS	
Chief complaint& duration	
History of presenting illness	
Medical history	
Dental history	
Oral hygiene	

IMPACTED THIRD MOLARS DETAILS		
Characteristics	**First visit**	**Second visit**
Group: I/II		
Sub-group: C/S		
Side: R/L		
Depth: A/B/C		
Angulation: H/M/D/V		
Position: Class I/Class II/Class III		

SURGICAL DETAILS		
Characteristics	**First visit**	**Second visit**
Date of surgery		
Number of dental cartridges		
Duration of surgery: min		
Bone removal: mild/moderate/sever		
Tooth sectioning: yes/no		

SURGICAL ASSESSMENT – FIRST VISIT		Pre Operative	Immediate	2nd Day	3rd Day	5th Day
Mouth Opening	Trismus					
Facial Swelling	From tragus of ear to corner of mouth					
	From tragus of ear to soft tissue pogonion					
	From lateral canthus of eye to angle of mandible					
Pain						

SURGICAL ASSESSMENT – SECOND VISIT		Pre Operative	Immediate	2nd Day	3rd Day	5th Day
Mouth Opening	Trismus					
Facial Swelling	From tragus of ear to corner of mouth					
	From tragus of ear to soft tissue pogonion					
	From lateral canthus of eye to angle of mandible					
Pain						

Appendix B: Participant Information Sheet

Study Title:

Comparison of Efficacy of Serratiopeptidase and Escin after Impacted Mandibular Third Molar Surgery: A Randomized Controlled Clinical Trial

Principal Investigator:

Arwa Mohammed Dahak
College of Dentistry, University of Science and Technology, Sana'a, Yemen
Telephone: 775163301
Email: hamddahak@gmail.com

Ethics Approval Reference:

University Research Ethics Committee Approval No. 1445/0012/UREC/UST
Date of Approval: 30/07/2024

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1. Introduction

You are invited to take part in a research study being conducted at the College of Dentistry, University of Science and Technology, Sana'a. Before you decide, it is important that you understand why the research is being carried out and what your participation will involve. Please take time to read this information carefully and ask the researcher if anything is unclear.

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2. Purpose of the Study

This study aims to compare the effectiveness of two medications—**serratiopeptidase** (an enzyme-based anti-inflammatory agent) and **escin** (a natural herbal compound derived from horse chestnut)—when used alongside conventional drugs to reduce **pain, facial swelling (edema), and limited mouth opening (trismus)** after the surgical removal of impacted mandibular third molars ("wisdom teeth").

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3. Why You Have Been Invited

You have been selected because you are medically healthy and require the extraction of both lower third molars (one on each side). Your participation will help determine which medication combination is more effective in improving postoperative recovery.

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4. Study Design and Procedures

- This is a **triple-blind, split-mouth randomized clinical trial**.
- Each patient will undergo **two surgical procedures**, one for each side of the lower jaw, separated by a **three-week washout period**.
- During one surgery, you will receive **conventional drugs only**; during the other, you will receive **conventional drugs plus either serratiopeptidase or escin**.
- All surgeries will be performed by the same oral surgeon using standard, safe techniques.
- You will be assessed before surgery and at several intervals after surgery (2nd, 3rd, and 5th postoperative days) for:
    - **Pain** (using a Visual Analogue Scale)
    - **Mouth opening (trismus)**
    - **Facial swelling (edema)**
- All evaluations are non-invasive and will not cause additional discomfort.

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5. Medications Used

All participants will receive standard postoperative care, including:

- **Amoxicillin 500 mg** twice daily
- **Metronidazole 500 mg** three times daily
- **Diclofenac sodium 50 mg** twice daily

Depending on your random group:

- **Group A:** Serratiopeptidase 10 mg, three times daily for 5 days

- **Group B:** Escin 20 mg, three times daily for 5 days

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6. Possible Benefits

Participation may help you experience reduced pain, swelling, and trismus after surgery. The findings may also benefit future patients undergoing similar procedures by improving postoperative management strategies.

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7. Possible Risks or Discomforts

The risks involved are minimal and similar to routine surgical removal of wisdom teeth, including:

- Pain, swelling, or mild bleeding
- Temporary limited mouth opening
- Rare allergic reactions to prescribed medications

All possible adverse reactions will be monitored and managed promptly by the research team.

8. Voluntary Participation and Right to Withdraw

Participation in this study is **entirely voluntary**.

You may choose not to participate or withdraw at any time without giving a reason. This will not affect your right to receive standard medical care. You may also refuse to answer any questions that make you uncomfortable.

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9. Confidentiality

All information collected during the study will remain **strictly confidential**. Your name will not appear in any publication or report. Data will be coded and stored securely, accessible only to the research team.

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10. Compensation and Costs

There are **no costs** to you for participation, and you will **not receive any financial compensation**. All treatments and medications related to the study will be provided free of charge.

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11. Ethical Approval

This study has been reviewed and approved by the **University of Science and Technology Research Ethics Committee**, which ensures that your safety, rights, and welfare are protected.

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12. Further Information and Contact Details

If you have any questions or concerns about the study, please contact:

- **Principal Investigator:** Dr. Arwa Mohammed Dahak – Tel: 775163301
- **Ethics Committee Representative:** Dr. Walid Al-Qudsi – Tel: 717163911

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13. Statement

By signing the Informed Consent Form, you confirm that you have read and understood this information sheet and agree to participate voluntarily in the study.

ورقة معلومات المشارك

عنوان الدراسة:

مقارنة مدى فعالية السيراتيوبيبتيداز والإسكين بعد جراحة الرحى الثالثة السفلية المنطمرة: تجربة سريرية عشوائية تحكمية

الباحثة: أروى محمد حسين دهاق

كلية طب الأسنان – جامعة العلوم والتكنولوجيا – صنعاء – اليمن
رقم الهاتف: 775163301
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رقم موافقة لجنة الأخلاقيات: 1445/0012/UREC/UST
تاريخ الموافقة: 30 / 07 / 2024

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1. المقدمة

ندعوك للمشاركة في هذه الدراسة البحثية التي تُجرى في كلية طب الأسنان بجامعة العلوم والتكنولوجيا – صنعاء. قبل أن تقرر المشاركة، من المهم أن تفهمي/تفهم سبب إجراء البحث وما الذي ستتضمنه مشاركتك فيه. الرجاء قراءة هذه المعلومات بعناية وطرح أي أسئلة على الباحثة إذا كان هناك ما هو غير واضح.

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2. هدف الدراسة

تهدف هذه الدراسة إلى **مقارنة فعالية دواءين** هما **السيراتيوبيبتيداز** (وهو إنزيم مضاد للالتهاب) و**الإسكين** (مستخلص عشبي طبيعي من نبات كستناء الحصان)، عند استخدامهما كمساعدين مع الأدوية التقليدية في **تقليل الألم، والانتفاخ الوجهي (الوذمة)، وتحدد الفتح الفموي (التريسمس)** بعد جراحة إزالة الرحى الثالثة السفلية المنطمرة (ضرس العقل السفلي).

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3. سبب اختيارك للمشاركة

تم اختيارك لأنك شخص سليم طبيًا وتحتاج إلى خلع الرحى الثالثة السفلية في الجهتين اليمنى واليسرى. مشاركتك ستساعد على معرفة أي من الدواءين أكثر فعالية في تحسين التعافي بعد الجراحة.

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4. تصميم الدراسة وإجراءاتها

- هذه الدراسة **عشوائية، مزدوجة التحكم، وثلاثية التعمية** لضمان الحيادية والدقة العلمية.
- سيُجرى لك **إجراءان جراحيان** في فكين مختلفين (اليمين واليسار) بفاصل زمني قدره **ثلاثة أسابيع**.
- في إحدى الجراحتين ستحصلين/تحصل على **الأدوية التقليدية فقط**، وفي الجراحة الأخرى ستحصلين/تحصل على **الأدوية التقليدية بالإضافة إلى السيراتيوبيبتيداز أو الإسكين**.
- ستُجرى جميع العمليات بنفس الطريقة بواسطة جراح فم واحد متمرس لضمان التوحيد والدقة.
- سيتم تقييم حالتك قبل الجراحة وبعدها في الأيام الثاني والثالث والخامس لقياس:

- **الألم** (باستخدام مقياس بصري من 0 إلى 10)
- **مدى فتح الفم (التريسمس)**
- **الانتفاخ الوجهي (الوذمة)**

- جميع القياسات غير مؤلمة ولا تتطلب أي تدخل إضافي.

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5. الأدوية المستخدمة

جميع المشاركين سيتلقون نفس العلاج التقليدي بعد الجراحة، وهو:

- أموكسيسيلين 500 ملجم – مرتين يوميًا
- ميترونيدازول 500 ملجم – ثلاث مرات يوميًا
- ديكلوفيناك صوديوم 50 ملجم – مرتين يوميًا

بالإضافة إلى أحد الدواءين التاليين وفقًا للمجموعة التي يتم اختيارك لها عشوائيًا:

- **المجموعة (أ) :**سيراتيوبيبتيداز 10 ملجم، ثلاث مرات يوميًا لمدة خمسة أيام.
- **المجموعة (ب) :**إسكين 20 ملجم، ثلاث مرات يوميًا لمدة خمسة أيام.

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6. الفوائد المحتملة

قد تساعد مشاركتك في تقليل الألم والانتفاخ وتحدد الفتح الفموي بعد الجراحة. كما ستُسهم نتائج هذه الدراسة في تحسين الرعاية المستقبلية للمرضى الذين يخضعون لإجراءات مشابهة.

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7. المخاطر المحتملة

المخاطر ضئيلة وتشبه تلك التي ترافق خلع ضرس العقل المعتاد، مثل:

- ألم أو تورم طفيف أو نزيف بسيط
- صعوبة مؤقتة في فتح الفم
- احتمال نادر لحدوث حساسية من أحد الأدوية

ستتم متابعة أي أعراض جانبية من قبل الباحثة ومعالجتها فورًا إن وجدت.

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8. الطوعية وحق الانسحاب

مشاركتك **طوعية تمامًا**.

يحق لكِ/لك الانسحاب من الدراسة في أي وقت دون ذكر الأسباب ودون أن يؤثر ذلك على حقك في تلقي الرعاية الطبية. كما يمكنك الامتناع عن الإجابة عن أي سؤال لا ترغب في الإجابة عليه.

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9. سرية المعلومات

جميع المعلومات التي يتم جمعها ستُعامل **بسرية تامة** .لن يُذكر اسمك في أي تقرير أو منشور بحثي. سيتم ترميز البيانات وتخزينها بشكل آمن ولن يطلع عليها سوى فريق البحث.

10.التعويض والتكاليف

لن تتحمل/تحملي أي تكاليف مقابل المشاركة في هذه الدراسة، ولن يتم تقديم أي مقابل مادي. جميع الأدوية والإجراءات المتعلقة بالدراسة تُقدَّم مجانًا.

11.الموافقة الأخلاقية

تمت مراجعة هذه الدراسة والموافقة عليها من قبل **لجنة أخلاقيات البحث العلمي بجامعة العلوم والتكنولوجيا**، والتي تضمن حماية حقوقك وسلامتك ورفاهيتك أثناء المشاركة.

12.لمزيد من المعلومات أو الاستفسار

إذا كان لديك أي أسئلة أو استفسارات حول الدراسة، يمكنك التواصل مع:

- **الباحثة الرئيسة:**
  د. أروى محمد حسين دهاق – هاتف: 775163301
- **عضو لجنة الأخلاقيات:**
  د. وليد القدسي – هاتف: 717163911

13.إقرار

بتوقيعك على **نموذج الموافقة المستنيرة**، فإنك تؤكد أنك قد قرأت هذه الورقة وفهمت محتواها، وأن مشاركتك في هذه الدراسة تتم بمحض إرادتك الحرة.

Appendix C: Informed Consent Form

Your signature on this statement means that you have read or listened to the data related to this research and that you agree to participate in the research. You will be given a copy of this statement to keep.

Right to Withdraw:

Your participation in this study is completely voluntary. You have the right to refuse to answer any question you do not wish to answer. You have the right to withdraw from the study without penalty and without affecting the level of medical care provided to you. You will be informed of any new information that emerges during the research period that may affect your desire to continue in the study.

General Conditions:

The researcher may stop your participation at any time for various reasons. These may be related to you personally, such as your condition being incompatible with the study, or external, such as the emergence of circumstances or alternatives to the study.

Confidentiality of the Research:

All information about you is strictly confidential. You will not be personally referred to at the end of the report and presentation of the results. It will not be used for any purpose other than scientific research. Only those responsible for conducting the research will know about your participation in the research.

If the participant has any questions, please contact:

Principal Investigator: Dr. Arwa Mohammed Dahak / Telephone: 775163301

Member of the College's Scientific Research Ethics Committee, Dr. Walid Al-Qudsi / Telephone: 717163911

Study Participant Consent:

I, the undersigned, declare that I have read, understood, and agreed to participate in the study and have reviewed the details.

Name: ……

Gender: □ Male □ Female

Address: …… Telephone: ……

Signature: ……..…… Date: ……

Researcher's Approval:

I pledge to maintain the confidentiality of the information of the research subject.

Researcher's Signature: …… Date: ……

نموذج الموافقة المستنيرة

توقيعك على هذا البيان يعني أنك قد قرأت أو استمعت إلى المعلومات المتعلقة بهذا البحث، وأنك توافق على المشاركة فيه. سيتم تزويدك بنسخة من هذا البيان للاحتفاظ بها.

الحق في الانسحاب:

مشاركتك في هذه الدراسة طوعية تمامًا. لك الحق في رفض الإجابة عن أي سؤال لا ترغب في الإجابة عنه، كما يحق لك الانسحاب من الدراسة في أي وقت دون أي عقوبة، ودون أن يؤثر ذلك على مستوى الرعاية الطبية المقدَّمة لك.

وسيتم إعلامك بأي معلومات جديدة قد تظهر خلال فترة البحث وقد تؤثر على رغبتك في الاستمرار بالمشاركة.

الشروط العامة:

يجوز للباحثة إيقاف مشاركتك في أي وقت لأسباب مختلفة، قد تكون متعلقة بك شخصيًا، مثل عدم توافق حالتك مع متطلبات الدراسة، أو لأسباب خارجية كظهور ظروف أو بدائل أخرى للدراسة.

سرية البحث:

جميع المعلومات المتعلقة بك ستُعامل بسرية تامة. ولن يتم الإشارة إلى اسمك أو شخصك في نهاية التقرير أو عند عرض النتائج. كما لن تُستخدم المعلومات إلا لأغراض البحث العلمي فقط.

وسيعلم بمشاركتك في البحث فقط الأشخاص المسؤولون عن تنفيذه.

في حال وجود أي استفسارات، يُرجى التواصل مع:

- **الباحثة الرئيسية:** د. أروى محمد دهاق — هاتف: 775163301
- **عضو لجنة أخلاقيات البحث العلمي بالكلية:** د. وليد القدسي — هاتف: 717163911

موافقة المشارك في الدراسة:

أقرّ أنا الموقّع أدناه بأنني قد قرأت وفهمت ووافقت على المشاركة في هذه الدراسة، وقد اطّلعت على جميع تفاصيلها.

الاسم: ..... الجنس: ☐ ذكر ☐ أنثى

العنوان: ..... رقم الهاتف: .....

التوقيع: ..... التاريخ: .....

إقرار الباحثة:

أتعهد بالحفاظ على سرية معلومات المشارك في البحث.

توقيع الباحثة: ..... التاريخ: .....