COVERING LETTER FOR RCT REGISTRATION

Submission Date: 15 November 2025

To

The Registration Officer

ClinicalTrials.gov

Subject: Submission of RCT for Registration

Dear Sir/Madam,

I am submitting my randomized controlled trial for registration on ClinicalTrials.gov.

Study Title: Role of Alprazolam in Management of Post-Endodontic Pain After Single-Visit Root Canal Treatment

This study is an interventional, two-arm randomized controlled trial evaluating postoperative pain management after single-visit root canal therapy. All required documents have been uploaded to the PRS system, and the study is ready for review.

Please process the registration at your earliest convenience. I will provide any additional information if needed.

Date of submission of research proposal: 15 November, 2025

NCT Number: *Not issued yet*

Unique Protocol ID: OD2025-PAIN-01

Ethical Committee Approval Number: EC2024-37

Department: Department of Operative Dentistry & Endodontics

AFID, Rawalpindi

Yours Sincerely,

Dr. Tahreem Qureshi

Principal Investigator

T.M.O Operative Dentistry & Endodontics

AFID, Rawalpindi

ROLE OF ALPRAZOLAM IN MANAGEMENT OF POST-ENDODONTIC PAIN AFTER SINGLE VISIT ROOT CANAL TREATMENT

Introduction

Root canal treatment is a complex procedure involving mechanical instrumentation of the root canal system, chemical debridement, and filling with an inert material to maintain or restore the health of peri-radicular tissues [1]. Its primary goal is to prevent or treat periapical disease while ensuring patient comfort throughout the procedure. However, achieving these objectives is often complicated by post-operative pain, a frequent and distressing outcome for patients [2].

Post-operative pain is a multifactorial phenomenon reported in 2.5% to nearly 60% of patients undergoing endodontic treatment. Pain prevalence tends to peak between 6 and 12 hours after treatment, affecting approximately 40% of patients within the first 24 hours and declining to about 11% one week later [3][4]. This pain is influenced by physiological and psychological factors, and failure to adequately manage it can result in poor patient cooperation, compromised outcomes, and reluctance to follow up on treatment. Thus, effective pain management is integral to endodontic success [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications for managing post-operative endodontic pain [6]. NSAIDs exert their effects by inhibiting Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) enzymes, thereby reducing the production of prostaglandins, which are critical mediators of inflammation and pain [7]. Despite their widespread use, NSAIDs may not fully address the psychological and emotional components of pain, which can exacerbate patient discomfort.

The role of anxiety in amplifying pain perception has been increasingly recognized. Studies suggest that benzodiazepines, such as alprazolam, could serve as adjuncts to NSAIDs by addressing the anxiety component of pain. Alprazolam, a benzodiazepine commonly prescribed for anxiety disorders, stimulates Gamma-aminobutyric acid (GABAA_AA) receptors in the dorsal horn of the spinal cord. This mechanism reduces pain-induced anxiety and stimulates the release of endogenous opioids like enkephalins in central nervous system areas involved in pain processing, resulting in an antihyperalgesic effect [8][9].

Mahmoud Baradaran et al. highlighted the potential of benzodiazepines to potentiate the analgesic effects of NSAIDs [10]. The VAS scores in alprazolam + ibuprofen group (2.33±1.05) were significantly lower at 6 hours after treatment when compared to the other group (Ibuprofen: 3.00±1.3). Given the dual mechanism of action of alprazolam, combining it with NSAIDs may offer a more holistic approach to managing post-endodontic pain. Moreover, a single dose of alprazolam is associated with minimal side effects, making it a safe and feasible option for this purpose [11]. The aim of this study is to discover whether a benzodiazepine agent such as alprazolam when used in combination with NSAIDs increases the analgesic efficacy of a non-opioid analgesic.

Despite advancements in pain management strategies, a significant proportion of patients continue to experience post-operative endodontic pain. Addressing the psychological dimensions of pain remains an unmet need in routine dental practice. This study seeks to explore whether alprazolam, a benzodiazepine with known anxiolytic and antihyperalgesic properties, can enhance the analgesic efficacy of NSAIDs. By investigating this combination, the study aims to provide a novel, evidence-based approach for improving pain management in endodontic treatment.

Objective of the Study

To compare mean pain score between two group of participants undergoing post operative pain management after single visit root canal treatment: one group receiving NSAIDs alone and the other receiving a combination of NSAIDs and an anxiolytic medication i.e alprazolam.

Operational Definitions

1. **Post-Endodontic Pain:**

The unpleasant sensory or emotional physical sensation a patient experiences after receiving a root canal is measured at certain intervals (first 6-, 12-, and 24-hours post-procedure).

2. **Visual Analogue Scale:**

A pain rating scale representing as a 10cm horizontal line with zero at one end which means ‘no pain’ and 10 on the other end which means ‘unbearable pain’. Patient is asked to mark on the scale corresponding to the severity of pain.

3. **Single-Visit Endodontics:**

The type of endodontic therapy that involves pulpectomy followed by chemo-mechanical preparation of the root canal system and three dimensional sealing of the pulp space with an inert material, all done on the same visit.

Hypothesis

The addition of alprazolam to non-opioid analgesics provides better post-endodontic pain relief, as measured by reduced standardized pain intensity scores at specific time intervals after the procedure.

Methodology

Study Setting
Department of Operative Dentistry, AFID Rawalpindi

Duration
6 months after approval

Study Design
Double-blind, Randomized-controlled trial

Sample Size
Using the WHO calculator where $\alpha = 0.05$ is the significance level, power = 80%, the sample size is estimated at n=110 having 55 participants per group. The mean pain scores were extracted from study done by Mahmoud Baradaran et. al at 6 hours interval in 2 groups: NSAIDs alone G1= 3 ± 1.36 and combination of NSAIDs and alprazolam G2= 2.33 ± 1.05 [10].

Sampling Technique
Consecutive Sampling Technique

Inclusion Criteria
- Patients aged between 18-60 years
- Healthy patients with ASA classification I and II
- Teeth with symptomatic irreversible pulpitis

Exclusion Criteria
- Patient suffering from a systemic disease that requires antibiotics
- Pregnant or lactating mothers
- Teeth with periapical radiolucency
- Single rooted teeth
- Teeth with severe periodontal disease
- Root canal treatment completed in multiple visits
- Patients who have taken analgesics 12-24 hrs before the procedure
- Patients already taking benzodiazepines

Data Collection Procedure

Study will be conducted after the approval of Institutional Ethics Review Committee, AFID (ANX "A"). (Attached at the end) A total of 110 patients reporting to Operative Dentistry Department, Armed Forces Institute of Dentistry will be invited for participation in this study.

The procedure will be explained to the patients and their parents in Urdu language and a written informed consent will be taken (ANX “B”).
Patients will be divided into two equal groups. Randomization will be carried out using a scientific random number table to ensure that the assignment to groups is unbiased. To minimize confounding variables, all patients will be matched based on relevant factors such as age, gender, and tooth location.
They will be screened for inclusion by taking history, performing relevant clinical examination and necessary tests along with peri-apical radiographs.
Single visit root canal therapy will then be initiated under local anesthesia (Septodent, Lignospan special, Lignocaine hydrochloride 2% and adrenaline 1:80 000) and rubber dam isolation. The treatment protocol will include taking working length 1mm short of radiographic apex with apex locator (DENTSPLY Maillefer, Denta Port ZX) and will be confirmed with periapical radiograph.
The root canals will be instrumented with ProTaper Universal hand files (DENTSPLY Sirona) under copious irrigation with 5.25% sodium hypochlorite (NaOCl) (Henry Schein Sodium hypochlorite solution) up to F2 protaper file (DENTSPLY Sirona).
Patency will be confirmed with a #10 K file (DENTSPLY maillefer) between each instrument change. The root canals will be flushed with 17% EDTA solution (ERKAMED Endo-prep Gel).
After chemo-mechanical preparation the canals will be dried using sterile paper points (Sure-endo). The teeth will be obturated the with endodontic sealer (President Dental Germany Endoplus) and core obturating material single cone F2 gutta percha (Bio GP points-sure endo). The apical extent of the master cone will be confirmed via periapical radiograph.
The canals will be coated with the sealer using lentulospiral (DENTSPLY Sirona) in a slow speed hand piece followed by the obturation of canals with single cone. F2 gutta percha (Bio GP points-sure endo, sure dent cooperation).
All the clinical procedures will be performed by single operator and the root canal procedure will be completed in single visit.
After obturation, access cavity is restored with atleast 4mm thick layer of Temporary filling (DETAX, Fermin) and patient will be recalled after 1 week for permanent filling.

Blinding will be implemented in the study to minimize bias.
For patient blinding, patients will be unaware of the study's focus on medication and its potential impact on post-operative pain. They will simply be told that the study investigates post-operative pain after RCT.
Operator Blinding will be achieved by having a single operator perform all clinical procedures and will be blinded to the post-operative pain assessment. A separate, blinded evaluator will administer the pain assessment and collect data to minimize bias.
To ensure outcome assessor blinding, the individual responsible for analyzing the pain scores and conducting the statistical analysis will be blinded to the group assignments (brufen vs brufen+alprazolam) to ensure unbiased outcome interpretation.

After obturation and temporary restoration, the patients will be randomly allocated into one of the two groups and given following analgesics;

Group 1 : ibuprofen 400mg (Abbot Brufen)
Group 2 : ibuprofen 400mg (Abbot Brufen) + alprazolam 0.5 mg (Hilton pharma Alp)

All the patients will be handed over a pain diary form with visual analogue scale (VAS) consisting of a 10 cm line divided into 10 equal parts from 0 indicating no pain to 10 indicating extremely severe pain. This provided a range of score from 0-10. The patients will be asked to record their pain response at 6 hrs, 12 hrs and 24 hrs after therapy followed by which the patients will be recalled to give the diary to the investigators on their follow up visit.

Statistical Analysis

Data analysis will be performed using SPSS version 23.0. The primary variable is post-operative pain, assessed using the Visual Analogue Scale (VAS) at 6, 12, and 24 hours after treatment. **Quantitative variables** such as age and VAS scores will be summarized using the mean, median, standard deviation, interquartile range, and range. **Qualitative variables** including gender, tooth location, and pre-existing dental conditions will be presented as frequencies and percentages.

An **independent samples t-test** will compare mean pain scores between groups at each time interval, while **repeated measures ANOVA** (or Friedman test for non-normal data) will evaluate changes in pain scores within groups over time. A p-value < 0.05 will be considered statistically significant. Confounding variables such as age, gender, tooth location, and pre-existing conditions will be controlled through stratification to ensure valid comparisons between groups.

References

1. Jou YT, Karabucak B, Levin J. Endodontic treatment and restoration of the endodontically treated tooth. Dent Clin North Am. 2020;64(4):737-750.
2. Di Spirito F, Scelza G, Fornara R, Giordano F, Rosa D, Amato A. Post-Operative Endodontic Pain Management: An Overview of Systematic Reviews on Post-Operatively Administered Oral Medications and Integrated Evidence-Based Clinical Recommendations. *Healthcare (Basel)*. 2022;10(5):760.
3. Alghamdi F, Alhaddad AJ, Almahdy A, Alzahrani S, Alzahrani A. Prevalence of postoperative pain after endodontic treatment using different sealers: A systematic review and meta-analysis. *Clin Oral Investig*. 2023;27(3):1235-1248.
4. Menke ER, Jackson CR, Bagby MD, Tracy TS. Efficacy and safety of postoperative medications in reducing pain after nonsurgical root canal treatment: A systematic review and network meta-analysis. *J Endod*. 2020;46(6):755-767.e3.
5. Masiulis S, Desai R, Uchanski T, Serna Martin I, Laverty D, Karia D, et al. GABA_A receptor signalling mechanisms revealed by structural pharmacology. *Nature*. 2019;565(7740):454-459.
6. Jang YE, Kim Y, Kim SY, Kim BS. Predicting early endodontic treatment failure following primary root canal treatment. *BMC Oral Health*. 2024;24:327.
7. Shamszadeh S, Shirvani A, Eghbal MJ, Asgary S. Efficacy of corticosteroids on postoperative endodontic pain: A systematic review and meta-analysis. *J Endod*. 2018;44(7):1057-1065.
8. Alghofaily M, Alharthi A, Alqedairi A, et al. Factors influencing non-surgical root canal treatment outcomes: a comprehensive review. *J Clin Med*. 2023;12(10):2931.
9. Almadi EM, Alghamdi FT, Alzahrani SA, et al. Efficacy of corticosteroids on postoperative pain levels after nonsurgical endodontic treatment: an overview of systematic reviews. *Saudi Endod J*. 2023;13(3):130-136.
10. Baradaran M, Hamidi MR, Moghimi Firoozabad MR, Kazemi S, Ashrafpour M, Moghadamnia AA. Alprazolam role in the analgesic effect of ibuprofen on postendodontic pain. *Caspian J Intern Med*. 2014;5(4):196-201.

11. Noor N, Azhar R, Sartaj R, Athar M. Severity of Post Obturation Pain in Single Versus Multiple Sittings Endodontic Treatment Using Rotary Nickel Titanium Instruments. *Pakistan Oral & Dental Journal*. 2023;43(3):156-160.

APPENDIX:

(ANNEX-A)

DEPARTMENT OF OPERATIVE DENTISTRY & ENDODONTICS

ARMED FORCES INSTITUTE OF DENTISTRY (AFID)

RAWALPINDI

CONSENT FORM

I, _____ **[Patient's Name],** hereby authorize **Dr. TAHREEM QURESHI** of the Department of Operative Dentistry, Armed Forces Institute of Dentistry, to perform Root Canal Therapy utilizing digital radiography and ultrasonic apex locator.

I have been fully informed about the entire procedure, including its potential success rates and risks of failure.

I confirm that the information provided to me was communicated clearly and comprehensively, enabling me to make an informed decision regarding this procedure.

I was given ample opportunity to ask questions, all of which were satisfactorily addressed.

Furthermore, I have been duly informed about the benefits of undergoing this treatment.

I understand that all treatments will be provided to me at no cost.

I willingly consent to undergo the treatment.

Patient's Signature: **Doctor's Signature:**

Date:

(ANNEX-B)

DEPARTMENT OF OPERATIVE DENTISTRY & ENDODONTICS

ARMED FORCES INSTITUTE OF DENTISTRY (AFID)

RAWALPINDI

S.No. _____ **Hospital Reg no: _____**

Gender: _____ **Age: _____**

Name: _____ **Contact number: _____**

Group: _____

Clinical Information (Effect Modifiers)

1. Tooth Number: _____

2. Tooth Location: _____

□ Maxillary □ Mandibular

□ Anterior □ Premolar □ Molar

3. Group: □ Group A □ Group B

4. Pre-Existing Dental Conditions (if any):

□ Periodontitis □ Apical Pathology □ None □ Other: _____

5. Consumption of analgesic before treatment (if any):

□ None

□ If yes, Name: _____ Frequency: _____

Groups	Pain after 6 hours using VAS	Pain after 12 hours Using VAS	Pain after 24 hours using VAS
A			
B			