Effect of Intracanal Cryotherapy and Metformin on Postoperative Pain in Teeth with Symptomatic Apical Periodontitis: A Randomized Clinical Trial

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Study Protocol and Statistical Analysis Plan

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Responsible Party

Principal Investigator

Ethics Committee Approval

Hamidiye Clinical Research Ethics Committee
University of Health Sciences
Approval No.: 13.02.2023–15184

Study Description

This document contains the complete study protocol and statistical analysis plan for a randomized, double-blind, 2×2 factorial clinical trial evaluating the effects of intracanal cryotherapy and intracanal medicaments on postoperative pain following root canal treatment.

UNIVERSITY OF HEALTH SCIENCES
HAMİDİYE CLINICAL RESEARCH ETHICS COMMITTEE

Evrak Tarih ve Sayısı: 13.02.2023-15184

T.C.
SAĞLIK BİLİMLERİ ÜNİVERSİTESİ
HAMİDİYE KLİNİK ARAŞTIRMALAR ETİK KURULU

Toplantı Tarihi : 19.01.2023
Toplantı Sayısı : 2023/1
Karar Sayısı : 23/1

Kurulumuza değerlendirilmek üzere sunduğunuz 22-123 kayıt numaralı "***Semptomatik Apikal Periodontitisli Dişlerde Farklı Kanal İçi Medikamentlerin ve Kanal İçi Kriyoterapi Uygulamalarının Endodontik Post-Operatif Ağrıya Etkilerinin İncelenmesi***" başlıklı proje önerisi kurulumuzun 19.01.2023 tarihli toplantısında uygun görülmüş olup, karar örneği ekte sunulmuştur.

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Study Protocol: Effect of Intracanal Cryotherapy and Metformin on Postoperative Pain in Teeth with Symptomatic Apical Periodontitis

1. Title

Effect of Intracanal Cryotherapy and Metformin on Postoperative Pain in Teeth with Symptomatic Apical Periodontitis: A Randomized Clinical Trial

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2. Study Objective

To evaluate the effects of intracanal cryotherapy and two intracanal medicaments (calcium hydroxide and metformin) on postoperative spontaneous and percussion pain in mandibular premolar teeth with symptomatic apical periodontitis.

Null hypothesis: No significant difference exists in postoperative pain among the study groups.

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3. Study Design

- Randomized, double-blind, 2×2 factorial clinical trial
- Parallel-group design with four groups:
    1. Calcium hydroxide
    2. Metformin
    3. Cryotherapy + calcium hydroxide
    4. Cryotherapy + metformin
- Duration: Postoperative follow-up for 7 days

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4. Ethical Approval

- Approved by Hamidiye Clinical Research Ethics Committee, University of Health Sciences (Approval No.: 13.02.2023–15184)
- Written informed consent obtained from all participants

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5. Sample Size Calculation

- Software: G*Power 3.1
- Effect size: f = 0.40
- Power: 0.90
- Significance level: α = 0.05
- Total sample: 80 patients (20 per group)

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6. Participants

Inclusion Criteria:

1. Systemically healthy
2. Mandibular premolars with pulpal necrosis requiring root canal treatment
3. Periapical index score 0–2
4. Age 18–70 years
5. Able to understand and complete VAS assessments
6. Provided written informed consent

Exclusion Criteria:

1. Systemic disease or pregnancy
2. Analgesic use within 24 hours prior to treatment
3. Severe bruxism
4. Acute apical abscess or swelling
5. Periodontal pocket >5 mm or tooth mobility > grade 1
6. Unrestorable teeth
7. Vital pulpal tissue or immature apices
8. Radiographic evidence of root resorption, root fracture, perforation, or canal calcification

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7. Randomization and Blinding

- Random sequence generated using Randomizer.org
- Allocation concealment by independent investigator
- Operator and patients blinded to:
    - Type of intracanal medicament
    - Presence/absence of cryotherapy

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8. Intervention

Root Canal Treatment Protocol:

- Local anesthesia: Articaine hydrochloride + epinephrine
- Rubber dam isolation
- Access cavity preparation
- Working length determination: Electronic apex locator + radiographic confirmation
- Canal instrumentation: ISO #40 apical size
- Irrigation:
    - 2 mL 5.25% NaOCl per instrument change
    - 5 mL 17% EDTA
    - Final rinse: 10 mL sterile saline over 5 min (4 °C in cryotherapy groups; 20 °C otherwise)
- Drying with sterile paper points

Intracanal Medicament Placement:

- Powder-to-liquid ratio: 1:1
- Lentulo spiral, 800 rpm, 20 s, 2 mm short of working length
- Groups 1 & 3: Calcium hydroxide
- Groups 2 & 4: Metformin
- Temporary restoration of access cavity

Cryotherapy Application:

- Final irrigation with sterile saline at 4 °C for cryotherapy groups (Groups 3 & 4)

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9. Outcome Measures

Primary Outcome:

- Postoperative spontaneous pain (VAS 0–100 mm), recorded pre-op and daily for 7 days

Secondary Outcome:

- Percussion pain (VAS 0–100 mm), assessed pre-op and post-op

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10. Statistical Analysis

- Software: R Statistical Software
- Significance: $\alpha = 0.05$

Analysis Plan:

- Spontaneous pain: Linear mixed-effects model for repeated measures
- Percussion pain: ANCOVA with preoperative pain as covariate
- Fixed effects: Time, cryotherapy, medicament type, and cryotherapy × medicament interaction
- Random effect: Patient

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11. Data Management

- Pain levels recorded by patients before any analgesic use
- Confidentiality maintained; individual patient data not shared publicly

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12. Follow-Up

- Pain assessment: Days 1–7 postoperatively
- No long-term follow-up in current study; suggested for future research

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13. Expected Results

- Intracanal cryotherapy expected to reduce postoperative pain
- Metformin effect on short-term pain expected to be comparable to calcium hydroxide
- No significant interaction anticipated between cryotherapy and medicament type

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14. Strengths and Limitations

Strengths:

- Randomized, double-blind, factorial design
- Standardized treatment protocol
- Appropriate statistical methods for repeated measures

Limitations:

- Short follow-up (7 days)
- Single-center study
- Subjective pain assessment (VAS)