

CORRELATION BETWEEN CLINICAL AND RADIOGRAPHIC SUCCESS FOLLOWING APEXOGENESIS IN IMMATURE PERMANENT FIRST MOLARS

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Abstract

Background: Preserving vital pulp tissue in immature permanent molars affected by deep caries is essential to encourage continued root maturation. Mineral trioxide aggregate (MTA) is a standard biomaterial, but alternatives like melatonin offer anti-inflammatory and odontogenic potential. This randomized clinical trial aimed to evaluate and compare clinical and radiographic outcomes following apexogenesis using melatonin, MTA, and their combination. **Methods:** Forty-five immature mandibular permanent first molars in children aged 6–8 years were randomly assigned to three groups (n=15 each): Group A (MTA), Group B (melatonin), and Group C (MTA + melatonin). Clinical parameters (pain, mobility, mucobuccal fold changes) and standardized digital radiographic outcomes (root lengths, apical foramen width, radicular dentin thickness, furcation radiodensity) were recorded at baseline, 1, 3, 6, 9, and 12 months post-operatively. Statistical evaluation included repeated-measures ANOVA, non-parametric tests, and Pearson correlation analysis. **Results:** High clinical success was observed at 12 months: Group C achieved 100%, while Groups A and B achieved 93.3% each, with no statistically significant intergroup differences. All successful cases showed continued apexogenesis. Pearson correlation and heatmap analysis demonstrated significant positive correlations between root length, dentin thickness, furcation radiodensity, and follow-up time. Root lengths correlated negatively with pain and mobility. Isolated failures revealed minor temporal discrepancies: MTA exhibited early clinical pain prior to radiographic signs, while melatonin presented radiographic arrest with minimal pain. **Conclusions:** Melatonin demonstrates clinical and radiographic efficacy comparable to MTA in apexogenesis. High concordant correlation confirms that clinical symptom resolution reliably mirrors radiographic physiological root development.

Keywords: Apexogenesis, Mineral Trioxide Aggregate (MTA), Melatonin, Immature Permanent Molars, Vital Pulp Therapy.

INTRODUCTION

Dental caries in young permanent teeth, particularly first permanent molars due to their early eruption and deep occlusal fissure anatomy, presents a frequent diagnostic and

therapeutic challenge in pediatric **endodontics** (Kontham et al., 2005; Damle, 2006; Taha et al., 2018). Deep carious lesions can cause irreversible pulp damage, pulpal necrosis, and the premature arrest of physiological root development (Nabi et al., 2015; Kahsay et al., 2025). Vital pulp therapy (VPT), specifically full pulpotomy for apexogenesis, aims to eliminate infected coronal pulp while preserving vital radicular pulp tissue to encourage continued root elongation, radicular dentin thickening, and apical closure (Chen et al., 2019; Sabeti et al., 2021; Zeng et al., 2024). Preserving vital pulp tissue maintains the tooth's natural proprioceptive, immunocompetent, and mechanical properties, significantly enhancing long-term tooth retention compared to conventional root canal treatment (Nabi et al., 2015; Murray et al., 2022; AlShareef, 2023).

Mineral trioxide aggregate (MTA) is widely regarded as the benchmark bio-inductive capping material in VPT owing to its biocompatibility, superior marginal seal, and ability to induce dentin bridge formation and hard tissue regeneration (Torabinejad et al., 1995; Moretti et al., 2008; Singh et al., 2020; AlShareef, 2023). However, conventional MTA presents well-documented clinical drawbacks, including prolonged setting times, difficult handling characteristics, high material costs, and potential crown discoloration (Schwendicke et al., 2015; Shafaroudi et al., 2018).

These limitations have spurred interest in novel biological therapeutics. Melatonin (N-acetyl-5-methoxy-tryptamine), a pleiotropic hormone, has emerged as a promising candidate due to its potent anti-inflammatory, antioxidant, and tissue-regenerative properties (Permuy et al., 2017; Gupta et al., 2024). Melatonin modulates the TLR4/NF- κ B pathway, reduces pro-inflammatory cytokine expression (IL-1 β , TNF- α), counteracts oxidative stress, and promotes the proliferation and odontogenic differentiation of human dental pulp cells (Li et al., 2015; Li et al., 2020). Preclinical animal studies suggest that melatonin exerts pulp-capping effects comparable to MTA (Guerrero-Gironés et al., 2020; Kermeoglu et al., 2021), yet clinical evidence evaluating its performance in immature permanent teeth post-apexogenesis remains scarce (Gupta et al., 2024).

Determining the definitive therapeutic outcome of VPT relies on rigorous diagnostic methodology and a direct correlation between clinical and radiographic evaluations (Shang et al., 2022; Asgary et al., 2024). Clinical success is characterized by the absence of persistent pain, mobility, swelling, sinus tracts, or tenderness to percussion, whereas radiographic success requires a normal periodontal ligament space, absence of internal or external root resorption, and continued physiological root maturation with dentin bridge deposition (Jafarzadeh et al., 2010; McHugh et al., 2023).

Successful VPT necessitates complete concordant harmony between both parameters, as progressive radiographic alterations like periapical lesions or root resorption may develop asymptotically without immediate clinical signs (Shang et al., 2022; Asgary et al., 2024). Analyzing the correlation between clinical parameters and radiographic outcomes is therefore vital to establish reliable diagnostic criteria and evaluate the overall clinical efficacy of novel pulp medicaments.

Accordingly, the aim of the present study is to evaluate and compare the pulp response of young permanent first molars after apexogenesis procedure with melatonin as a new medicament versus MTA, both clinically and radiographically.

MATERIALS AND METHODS

Ethical Approval and Study Design This randomized clinical trial (RCT) evaluated 45 young mandibular permanent first molars in 45 children attending the outpatient clinic of the Pediatric Dentistry Department, Suez Canal University. The study protocol was approved by the Institutional Research Ethical Committee (REC No. 569/2022), registered at ClinicalTrials.gov (NCT06372561), and performed in accordance with institutional guidelines. Informed written consent was obtained from parents or legal caregivers prior to execution.

Sample Size and Randomization Sample size calculation was performed using G*Power software version 3.1.9.6 (Cohen, 1988; Faul et al., 2013; Guerrero-Gironés et al., 2020). For a two-way repeated-measures ANOVA, a minimum sample size of 36 molars was required to detect an effect size of 0.25 at 95% power ($1 - \beta = 0.95$), $\alpha = 0.05$, and partial $\eta^2 = 0.06$. To compensate for an expected 25% dropout rate, 45 molars were enrolled. Teeth were randomly allocated in a 1:1:1 ratio using www.randomizer.org and paper lottery (Kahan et al., 2015) into three equal groups ($n = 15$ each): Group A (MTA), Group B (Melatonin), and Group C (MTA + Melatonin).

Clinical Apexogenesis Procedure Following pre-operative cold pulp testing and local anesthesia via inferior alveolar nerve block (Khalil, 2014), teeth were isolated using a rubber dam. Caries was excavated, and coronal pulp tissue was amputated under water cooling. Hemostasis was achieved using 5% NaOCl for up to 10 minutes (AAE, 2021).

Sub-base dressings (0.5–2 mm thickness) were placed over pulp stumps (Daniele, 2017). MTA mixed with saline for Group A; 20 mg melatonin powder mixed with 0.1 mL saline paste for Group B (Rostom et al., 2020); and half-dose MTA with 10 mg melatonin powder in 0.1 mL saline for Group C. Cavities were sealed with glass ionomer cement (Fuji IX) and restored with composite resin.

Clinical and Radiographic Assessment Evaluations occurred at baseline, 1, 3, 6, 9, and 12 months post-operatively (El-Khodary et al., 2014; AAPD, 2023). Treatment was deemed clinically successful in the absence of spontaneous pain, pain on percussion (modified Visual Analogue Scale), mucobuccal fold changes (redness, swelling, sinus tract), and pathic tooth mobility (Miller classification; Miller, 1985).

Standardized digital periapical radiographs were acquired using the Rinn XCP paralleling technique at 70 kV, 7 mA, and 0.125 s. Radiographs were analyzed using ImageJ software (version 1.44p) (Mahfouz et al., 2021) by a blinded observer in duplicate at two-week intervals.

Evaluated Radiographic Parameters (Smail Et Al., 2018) Included

1. Linear mesial and distal root lengths (mm).
2. Apical foramen width (mm).
3. Radicular dentin thickness 5 mm apical to the CEJ (mm).
4. Mid-furcation dentin radiodensity (256-grey scale within a 2×2 cm square).

Statistical Analysis and Parameter Correlation Data analysis was conducted using IBM-SPSS (version 26.0). Normality was verified via Shapiro-Wilk tests. Group and longitudinal differences were analyzed using two-way repeated-measures ANOVA followed by Duncan multiple range tests (DMRT), or Kruskal-Wallis tests for non-parametric data. Paired t-tests evaluated mesial versus distal root changes, while Kaplan-Meier curves determined material survival rates.

To evaluate the degree of association between clinical symptoms and objective radiographic outcomes, Pearson's correlation coefficients were calculated across all clinical parameters (pain scores, mobility grades, vestibular changes) and quantitative radiographic findings (root elongation, apical narrowing, dentin wall thickening, and furcation radiodensity). A red-blue correlation heatmap was constructed to visually map and identify significant positive and negative correlation patterns across variables.

RESULTS

I-Demographic Data:

Age and Gender Distribution of the Patients

- The age of patients in the study was 6-8 years old, with mean age almost 7 years.
- Regarding gender, the study included 45 patients (26 females and 19 males).

There was no statistically significant difference between the gender or the number of females and males in the total study sample or within each group as seen in **Table (1)** and **Fig (1)**.

Table 1: Age and Gender Distribution in the Three Study Groups

Gender and Age per groups						
	Gender		Chi square P value	Mean Age		T test P value
	Male	Female		Male	Female	
MTA	6 (40%)	9 (60%)	0.438ns	7.3 (0.7)	7.1(0.69)	0.831ns
Melatonin	5 (33.3%)	10 (66.7%)	0.196ns	7.0 (0.65)	7.2(0.55)	0.874ns
Mixed	8(53.7%)	7(46.7%)	0.796ns	7.2(0.48)	7.1(0.53)	0.953ns
Total	19 (42.2%)	26(57.8%)	0.296ns			
Chi square P value	0.688	0.760				

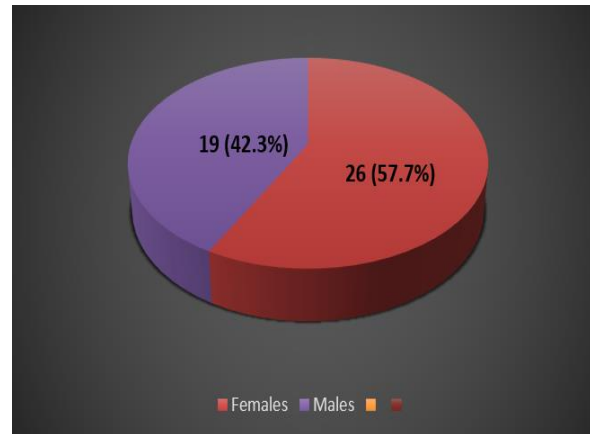


Figure 1: Pie Chart Representing Gender Distribution Among The Patients

Clinical Success of Clinical Variables

Mixed group (Group III) showed the highest success rate 100%, followed by the other two groups (MTA and Melatonin) with an overall success rate of 93.3% in each group. Although group III showed the higher success, there was a non-significant difference between the three groups regarding the clinical variables' success (**Table 2**).

Table 2: Success Rate in Clinical Parameters

Time	Clinical Success rate (%)						Kruskal-Wallis
	G1 (MTA group)		G2 (Melatonin group)		G3 (MTA and Melation group)		
	N	%	N	%	N	%	
1 month	15	100.0	15	100.0	15	100	>0.999 ns
3 months	15	100.0	15	100.0	15	100	>0.999ns
6 months	14	93.3	15	100.0	15	100	0.386 ns
9 months	14	93.3	14	93.3	15	100	0.600 ns
12 months	14	93.3	14	93.3	15	100	0.600 ns

*, **, *** significant at $p < 0.05$, < 0.01 , < 0.001 ; ns, nonsignificant at $p > 0.05$

Correlation between Clinical and Radiographic Results

Table (3) represents Pearson's correlation coefficient between study variables. Moreover, **Figure (2-3)** represents a red-blue correlation heatmap is a graphical representation used to visualize the correlation between pairs of variables in a dataset. It's often used in data analysis to quickly identify patterns of positive and negative correlations among variables. The color scale typically ranges from red (indicating negative correlation) through white (indicating no correlation) to blue (indicating positive correlation). The heatmap is a grid where each cell represents the correlation between two variables. The row and column of a cell correspond to the two variables being compared. The diagonal of the heatmap usually contains cells that represent the correlations of each variable with itself, which is always perfect (correlation value of 1). Furthermore, the intensity of the color in a cell indicates the strength of the correlation. Darker shades of blue or red indicate stronger correlations, while white cells represent no

correlation. Interpretation by examining the colors in the heatmap, you can quickly identify which variables are positively correlated (bluish cells), which are negatively correlated (reddish cells), and which have little to no correlation (white cells).

According to Correlation matrix and heatmap, distal and mesial root lengths, width of radicular dentin, and density of furcation dentin showed a direct positive significant correlation with Time as overall relationship.

In addition, pain incidence score showed positive direct significant relationship with pain on percussion score, mucobuccal folds' changes and mobility. The distal/mesial root lengths were negatively correlation with pain incidence, pain on percussion, mucobuccal folds' changes and mobility.

Table 3: Pearson's Correlation Matrix Presenting the Correlation Coefficient, And Two Tailed Significance Tests between Study Variables

Parameters	Distal root length	Mesial root length	WAF Distal	WAF Mesial	WRD Distal	WRD Mesial	Density of furcation dentin	Time	Group
Root length-Distal		0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00
Root length-Mesial	0.70		0.00	0.00	0.00	0.00	0.21	0.00	0.17
WAF-Distal	-0.46	-0.45		0.00	0.00	0.00	0.00	0.00	0.00
WAF-Mesial	-0.44	-0.57	0.86		0.00	0.00	0.00	0.00	0.01
WRD-Distal	0.38	0.39	-0.20	-0.35		0.00	0.00	0.00	0.00
WRD-Mesial	0.48	0.30	-0.35	-0.27	0.60		0.00	0.00	0.00
DFD	0.15	0.07	-0.35	-0.38	0.35	0.17		0.00	0.50
Time	0.39	0.36	-0.42	-0.49	0.42	0.32	0.65		1.00
Group	0.29	0.08	-0.25	-0.15	0.18	0.24	0.04	0.00	

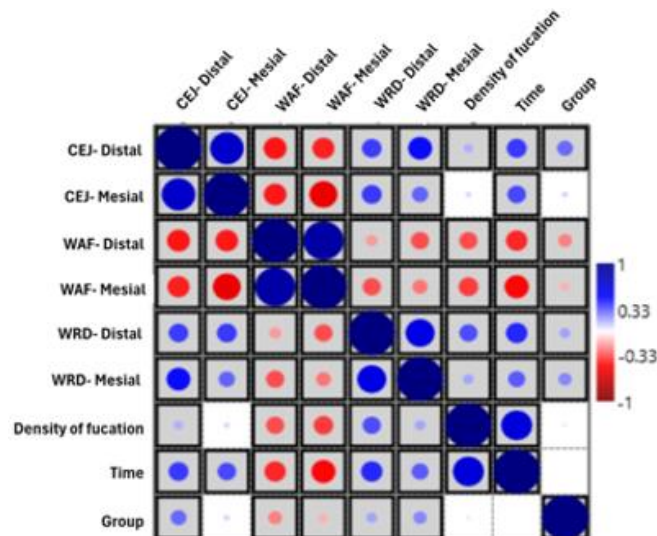


Figure 2: Blue-Red Heatmap Presenting the Interrelation between Study Variables, Blue Indicate Position Correlation, Red for Negative Correlation, White for No Correlation, Grey Boxed Color for Significant Correlation

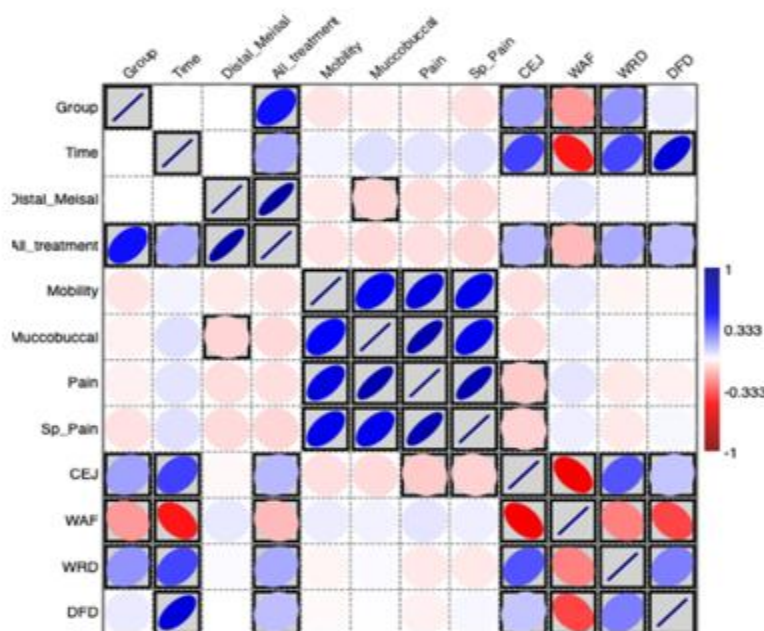


Figure (3). Blue-Red Heatmap Presenting the Interrelation between Study Variables, Blue Indicates Position Correlation, Red for Negative Correlation, White for No Correlation and Grey Boxed Color for Significant Correlation

DISCUSSION

The clinical success of vital pulp therapy (VPT) hinges on accurate preoperative diagnosis, strict aseptic protocols, effective hemorrhage control, and a durable coronal seal to prevent microleakage (**Careddu et al., 2021; AlShareef, 2023; Duncan et al., 2023**). In the present study, clinical outcomes were monitored using key parameters including spontaneous pain, pain on percussion, mucobuccal fold changes, and tooth mobility (**Igna et al., 2022; Mendes et al., 2025**). Radiographic success was evaluated via standardized digital periapical radiographs to trace linear increases in mesial and distal root lengths, thickening of radicular dentin, narrowing of apical foramina, and increases in furcation dentin density (**Belli et al., 2015; Kurlyo et al., 2024**).

Overall, the investigation demonstrated high clinical and radiographic success rates across all study cohorts: Mineral Trioxide Aggregate (MTA; Group I), Melatonin (Group II), and the combination of MTA and Melatonin (Group III). Radiographically, all successful cases displayed continued apexogenesis. The MTA and combination groups exhibited the highest percentage increases in root length, closely followed by the Melatonin group, with no statistically significant differences among the three groups. Similar non-significant, equivalent improvements across groups were observed for apical foramen narrowing, radicular dentin thickening, and furcation dentin mineral density. These favorable outcomes reflect MTA's bioactive properties, high alkalinity, and hydrogel hydroxyapatite-forming capabilities (**Abuhashema et al., 2025; Karunakaran et al., 2025**), alongside

Melatonin's immunomodulatory, anti-inflammatory, and epigenetic effects on dental mesenchymal stem cell differentiation (**Wang et al., 2016; Li et al., 2020; Sanidhya et al., 2025**).

Based on heatmap analysis, a strong, consistent correlation was established between clinical and radiographic parameters throughout the 12-month follow-up. Clinical success predominantly aligned with positive radiographic signs of hard tissue regeneration and apical closure. However, minor temporal discrepancies between clinical manifestations and radiographic observations were identified in isolated failure cases:

Early Clinical Manifestation without Radiographic Changes: In the MTA group, a single failure case presented at the 6-month recall with acute clinical failure—specifically spontaneous pain and severe mucobuccal fold redness—prior to visible radiographic pathosis. This temporary divergence occurs because early bacterial infection and localized periapical micro-inflammation stimulate pulpal and periodontal nerve endings, producing clinical symptoms before sufficient mineral loss occurs to manifest radiographically (**Castillo et al., 2021; Steven, 2022; Blake et al., 2023**).

Radiographic Progression with Modulated Symptoms: In contrast, the failure case within the Melatonin group manifested at the 9-month follow-up with clear radiographic arrest of root development alongside only mild, provoked pain.

This pattern underscores how Melatonin's inherent analgesic, anti-inflammatory, and neuro-modulatory properties may alter subjective pain perception, masking early symptomatic inflammation even as radiographic changes proceed (**Sanidhya et al., 2025; Blake et al., 2023**).

Despite these subtle temporal variations in failure onset, Kaplan-Meier survival analysis demonstrated equivalent long-term survival rates for MTA, Melatonin, and their combination. Ultimately, the overall strong correlation between non-invasive clinical indicators and objective digital radiographic measurements confirms that absence of clinical symptoms (pain, mobility, soft tissue lesions) reliably reflects underlying pulpal healing, hard tissue deposition, and successful apexogenesis.

In addition to its ability to promote the release of bioactive dentin matrix proteins, the MTA group's clinical success may also be attributed to its bioactivity, low solubility, radiopacity, hydrophilicity, and sealing capability, which may also account for its decreased antibacterial efficacy. This can be explained by its post-setting expansion due to crystal growth and precipitation of apatite-like crystals at the MTA-dentine interface and within dentine collagen fibrils, which enhance push-out bond strength by creating chemical and mechanical. Because MTA is hygroscopic, it releases calcium ions, which are thought to be necessary for the creation of dentin bridges. Additionally, the release of calcium ions causes a hydroxyapatite layer to form when it comes into touch with tissue fluids, which promotes the growth of reparative dentin. Deeper insights into the quality of dentin bridge development were obtained through histological examinations (**Abuhashema et al., 2025; Karunakaran et al., 2025**).

The success of melatonin may be also returned to antioxidant effects of melatonin, and it's confirmed by Keskin *et al.* ⁽³⁹⁾ who explained that the formation of dentin-bridge beneath melatonin may be returned to its antioxidant and anti-inflammatory effects.

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