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Original Article

Evaluation of the Effect of Propolis versus Calcium Hydroxide, Intracanal Medicaments, on Post-Operative Pain in Patients with Necrotic Pulp: A Randomized Clinical Trial

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Abstract

Aim: The aim of this parallel single-blinded randomized clinical trial was to evaluate propolis (a flavonoid-rich, resinous product of honeybees) versus calcium hydroxide, intracanal medicaments, on post-operative pain in patients with necrotic single canal teeth.

Methods: Forty-six participants, aged 20-40 years, with asymptomatic necrotic pulp, single-root, single canal teeth were equally randomized into 2 groups; calcium hydroxide (control, Metapaste) and propolis (intervention). Root canal treatment was done with Protaper Universal and NaOCl 2.5% and EDTA 17% irrigants in two visits. Intracanal medicament was applied at the end of the first visit for one week in between. Participants rated their pain on a numerical rating scale (NRS) at 24, 48, 72 hours and at 7 days after medicament application. Obturation was done after the second visit. Inter-group data were compared and analyzed using Chi square, Bonferroni and t-tests. Numerical rating scale scores were presented as median and range values. The significance level was set at $P \leq 0.05$.

Results: The incidence of post-operative pain between both groups showed no statistically significant difference at different time intervals ($p>0.05$). There was a non-significant, gradual decrease in post-operative pain intensity in both propolis ($P=0.17$) and calcium hydroxide ($P=0.274$) groups, at different time intervals.

Conclusions: The intracanal use of both calcium hydroxide and propolis were equally effective in controlling post-operative pain. Propolis can be used as an alternative intracanal medicament to calcium hydroxide paste.

Keywords: Propolis, Calcium Hydroxide, Post-Operative Pain, Randomized Clinical Trial

Introduction

Calcium hydroxide ($Ca(OH)_2$) is the most widely used intracanal medicament; its high alkalinity accounts for its antimicrobial action, organic tissue dissolution capability and anti-inflammatory effects (Safavi et al., 1990; Zehnder et al., 2003). $Ca(OH)_2$ decreases the amount of bacteria present in root canals (Shuping et al., 2000), however, the buffering action of dentine neutralizes the action of $Ca(OH)_2$ resulting in the survival of microorganisms (Haapasalo et al., 2000). $Ca(OH)_2$ has a detrimental effect on periodontal tissues (Hauman & Love, 2003) and is not effective in eliminating *Entercoccus faecalis*, which is the bacterium associated with persisting endodontic infections (Safavi et al., 1990), since it could survive and buffer the high alkalinity of $Ca(OH)_2$ (Haapasalo et al., 2000). Due to the controversy concerning its efficacy as an intracanal medicament, natural products, such as propolis, are now being introduced (Bankora et al., 1983).

Propolis is an immunomodulatory, antioxidant, flavonoid-rich resinous product of honeybees (Bankora et al., 1983). It has been used in dentistry as an anticaries agent (Ikeno et al., 1991), pulp capping agent (Sabir et al., 2005), a storage medium for avulsed teeth (Martin & Pileggi, 2004) and a sealant for dentinal hypersensitivity (Almas et al., 2001). It was reported that propolis is less cytotoxic (Al-shaher et al., 2004) and more effective against resistant microorganisms than $Ca(OH)_2$ as well as biocompatible to the periradicular tissues than existing intracanal medicaments (Kandaswamy et al., 2010). Until now, there are very few randomized clinical trials that have examined the efficacy of propolis as an intracanal medicament on post-operative pain; therefore, the aim of this trial was to compare the effect of propolis and $Ca(OH)_2$, intracanal medicaments, on post-operative pain in patients with necrotic, single canalled teeth.

The null hypothesis of this trial was that there was no difference between propolis and $Ca(OH)_2$ as intracanal medicaments on post-operative pain in patients with necrotic, single canalled teeth.

Materials and Methods

This self-funded, parallel randomized clinical trial was approved by the Human Subjects Review and Ethics Committee of Cairo University of Dentistry. This trial is registered at ClinicalTrials.gov, number NCT04983524.

A power analysis was based on previous studies, *Ehrmann et al* (Ehrmann et al., 2003) and *Singh et al* (Singh et al., 2013). In which a sample size of 23 in each group would be required to detect an effect size of 0.2, a power of 80%, a significance level of 5% considering non-parametric distribution of the outcome variable.

Patients were recruited from the Outpatient Endodontic Clinic at the Faculty of Dentistry, Cairo University to meet the target sample size. All 46 adult participants were in the age range of 20-40 years old, medically-free of systemic diseases determined by a written questionnaire and oral questioning. Participants were included in the trial if they had necrotic, mature single canalled maxillary and mandibular teeth with periapical involvement as widening in the periodontal membrane space. Exclusion criteria were: pregnant or lactating females, root resorption or anatomic abnormalities, teeth with cracks, curvatures, root caries, calcified canals, the presence of periapical swelling, sinus tracts, acute periapical lesions and previously endodontically-treated teeth. A written consent was obtained from each participant.

Diagnosis, based on history-taking which revealed intensity, nature, quality, onset, location, duration, course, initiating and relieving factors

of pain in the patient's own words. Clinical examination revealed that all participants had no pre-operative pain and a negative response to palpation, percussion and hot and cold tests. Radiographic examination confirmed that all participants with periapical infection presented as radiolucency or widening in the periodontal membrane space were included in the study.

The participants recorded their pain level on a Numerical Rating Scale (NRS) (McCaffery et al., 1989) scale. It is an 11-point scale in which participants were asked to mark on the number that represented their level of pain. Afterwards pain was divided into four pain categories: no (0), mild (1–3), moderate (4–6), and severe (7–10). All participants had no pre-operative pain.

A random sequence generator by Microsoft Excel denoted intervention and control as A and B and kept with the co-supervisor. This trial was single-blinded, where the participant was blind to the assigned intervention.

Preparation of Propolis to be used as intracanal medication: (Üstün et al., 2013)

1. 250g of crude propolis (Propolis, Imtenan Corporate Headquarters is in Obour City, Egypt) powder was macerated in 70% ethyl alcohol and kept for 2 weeks in the dark at room temperature.
2. The aqueous ethanolic extract was filtered through Whatman filter paper no. 1. (Whatman,GE Healthcare,US)
3. Step 1 and 2 were repeated. The resulted filtrates were combined and evaporated using a rotary evaporator (Heidolph rotary evaporator, Heidolph, Germany) at 50°C under thermal, mechanical and reduced pressure.
4. The resulted viscous extract was manipulated by distilled water and alcohol then dried in an oven under vacuum (Vaco Term,J.P Selecta, Spain) at 50°C until a creamy consistency was reached.
5. The resulted mixture was rendered radio-opaque by 15% barium sulfate.

At the first appointment: The tooth was accessed and checked to be out of occlusion then isolated with a rubber dam. Working length was determined by an electronic apex locator (Root ZX mini, J MORITA, Tokyo, Japan) and confirmed by a periapical radiograph. Cleaning and shaping were done using a hybrid technique with preflaring using SX at coronal two thirds for establishing a straight-line access. Protaper Universal rotary NiTi system (Dentsply Maillefer, Ballaigues, Switzerland) was used for apical preparation (operated according to manufacturer's instructions). The sequence of the canal preparation started with S1, S2, F1 till F5 used to the full working length and then the master apical cone was selected accordingly.

Irrigation sequence: 1ml of 2.5% NaOCl was irrigated and manually agitated between every two files delivered by a 28-gauge disposable plastic needle with a side-vented tip (Steri-pro Tips, DiaDent Group International, Chungcheongbuk-do, Korea) inserted 1mm shorter than the working length. Final irrigation sequence was done by 5ml 2.5% NaOCl then 5ml normal saline and finally 5ml 17% EDTA solution (Prevest Denpro Limited, Digiana, India). The canal was then dried using paper points before medicament application.

Intervention: The co-supervisor was phone-called to assign the participant to either group according to the generated random sequence.

Intervention group (23 participants)

1. Propolis paste was injected inside the canal using a long disposable tip 3mm less than working length and then checked with periapical radiograph.

Control group (23 participants)

2. $Ca(OH)_2$ Metapaste is a ready-made paste in a plastic syringe. It was injected in an apico-coronal direction inside the canal 3mm less than

the full working length withdrawing slowly using its long disposable tip (METABIOMED.CO., LTD, Korea) and checked with periapical radiograph to avoid accidental apical extrusion. Both medicaments were kept in the canal for one week.

Resin-modified glass ionomer capsule was used as a temporary filling material to ensure proper sealing and no leakage. The participant was given the NRS to assess the pain at 24, 48 and 72 hours post-operatively.

If a participant experienced interappointment flare-up pain, he was allowed to take a non-steroidal anti-inflammatory drug every 8 hours (Cataflam 50mg). However, if the pain was too severe with/without swelling, then an emergency visit was done and antibiotics were prescribed (Hibiotic 1gm/12x5 or Dalacin C 300mg cap/8x5 if allergic to penicillin). *Emergency visit:* The medicament was removed and the apical constriction was violated by K-file #25 (if no drainage occurred). Irrigation with warm saline was done when there was pus/exudate then by 5ml 2.5% NaOCl followed by 5ml saline then by 5ml 17% EDTA solution. The canals were dried with paper points and medicament was re-applied. In all flare-up cases, pain was recorded normally. They were included in the trial, recorded as flare-up cases and was stated that the medicament was reapplied.

At the second appointment (Day 7): Pain was assessed by the participant on the NRS before obturation. After obturation, the participant was referred for restoration.

Statistical analysis: Categorical data was presented as frequencies (n) and percentages (%). Chi square test was used for statistical analysis followed by pairwise comparisons utilizing z-test with Bonferroni correction when the main test was significant. Quantitative data was explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. Age of the participants showed normal distribution, so it was presented as mean and standard deviation (SD) values and was analyzed using Independent t-test. Non-numerically-distributed numerical rating scores (NRS) were presented as median and range values and was analysed using Mann Whitney U test for intergroup comparisons and Friedman test of repeated measures followed by multiple pairwise comparisons utilizing Wilcoxon signed-ranks test with Bonferroni correction for intragroup comparisons when the main test was significant. The significance level was set at $P \leq 0.05$ for all tests. Statistical analysis was performed with IBM® SPSS® (SPSS Inc., IBM Corporation, NY, USA) Statistics Version 25 for Windows. The data was statistically analyzed by multivariate analysis and t-test.

Results:

There were 54 adult participants assessed for eligibility in this clinical trial; 46 were included and eight were excluded for not meeting the inclusion criteria. All participants completed the study, were included in the analysis and were analyzed statistically.

Baseline demographic data, presented in Table 1, of age, gender and tooth type had no statistically significant difference in their distribution of both groups.

In the propolis group, there was a gradual non-significant decrease in the distribution of pain scores between different time intervals at each category (P=0.17). The highest incidence of ‘no pain’ was found at 7 days; ‘mild pain’ was found at 48 hours and ‘moderate’ and ‘severe’ pain were found at 24 hours.

In the calcium hydroxide group, there was a gradual non-significant decrease in the distribution of pain scores between different time intervals (P=0.274). The highest incidence of ‘no pain’ was found at 7 days; ‘mild pain’ was found

at 48 hours, 'moderate pain' was found at 24 hours and 'severe pain' was found equally at 24 and 48 hours.

The incidence of post-operative pain between both groups, presented in Table 2, showed no statistically significant difference at different time intervals (p>0.05). 0.774 at 24 hours; 0.793 at 48 hours; 1.000 at 72 hours and 0.600 at 7 days.

The intensity of post-operative pain showed no significant difference in median and range values of NRS scores between both groups for all time intervals: 0.930 at 24 hours; 0.928 at 48 hours; 1.000at 72 hours and 0.555 at 7 days. $Ca(OH)_2$ group (P=0.518), propolis group (P=0.730) as seen in Table 3.

Table (1): Baseline demographic data

Baseline demographic	Propolis (n %)	$Ca(OH)_2$ (n%)	P-Value
Male	7 (30.4%)	7 (30.4%)	0.625
Female	16 (69.6%)	16 (69.6%)	
Mean Age (y)	31.82 ±9.95	35.43 ±9.31	0.211
Anterior	21 (91.3%)	20 (87%)	0.5
Premolar	2 (8.7%)	3 (13%)	

Table (2): Frequencies (n) and percentages (%) comparing incidence of post-operative pain categories between both groups at different time intervals

Time interval	Pain category	Propolis		Calcium hydroxide		P-value
		%	(n)	%	(n)	
24 hours	*None*	60.9%	(14)	60.9%	(14)	0.774ns
	Mild	21.7%	(5)	17.4%	(4)	
	Moderate	8.7%	(2)	17.4%	(4)	
	Severe	8.7%	(2)	4.3%	(1)	
48 hours	*None*	69.6%	(16)	65.2%	(15)	0.793ns
	Mild	26.1%	(6)	26.1%	(6)	
	Moderate	0%	(0)	4.3%	(1)	
	Severe	4.3%	(1)	4.3%	(1)	
72 hours	*None*	78.3%	(18)	78.3%	(18)	1.000ns
	Mild	17.4%	(4)	17.4%	(4)	
	Moderate	4.3%	(1)	4.3%	(1)	
	Severe	0%	(0)	0%	(0)	
7 days	*None*	95.7%	(22)	91.3%	(21)	0.600ns
	Mild	4.3%	(1)	4.3%	(1)	
	Moderate	0%	(0)	4.3%	(1)	
	Severe	0%	(0)	0%	(0)	

Table (3): Median and range values of NRS for post-operative pain for both groups and time intervals

Time interval	Post-operative pain [median (range)]		P-value
	Propolis	Calcium hydroxide	
24 hours	0.60 (10.00)	0.56 (7.00)	**0.930ns**
48 hours	0.44 (8.00)	0.42 (7.00)	**0.928ns**
72 hours	0.23 (4.00)	0.23 (4.00)	**1.000ns**
7 days	0.08 (2.00)	0.09 (4.00)	**0.555ns**
P-value	**0.730ns**	**0.518ns**	

*; significant ($p \leq 0.05$) ns; non-significant ($p>0.05$)

Discussion:

Necrotic pulp with asymptomatic periapical infection contains microorganisms that produce enzymes and endotoxins causing persistent painful periapical lesions (Dahlen & Bergenholtz, 1980). Therefore, intracanal use of medicaments is necessary for eradicating these microorganisms.

Propolis has been proven to have antimicrobial activity against polymicrobial cultures collected from necrotic root canals. (Al-shaher et al., 2004)

The NRS was used in this study as it is easy to use, reliable and generates data that can be statistically analyzed; additionally, NRS is more sensitive to small changes than simple descriptive ordinal scales (Williamson & Hoggart, 2005). NRS quantitatively evaluated pain intensity at four stages giving enough time for symptoms to subside after chemomechanical preparation (Pak & White, 2011). Pain perception and intensity are multifactorial, therefore, quantifying and standardizing pain objectively across a group of individuals can be challenging. NRS is traditionally used for quantitative analysis of pain (Ferreira-valente et al., 2011).

The crown-down technique with engine-driven Ni-Ti systems was used in the present study to reduce or prevent post-operative pain of necrotic teeth like: minimal extrusion of debris and less probability for flare-ups which is in agreement with (Aksel et al., 2017; Kuştarcı et al., 2008). Preflaring with SX was also done to reduce the amount of apically extruded debris (Borges et al., 2016) as well as reducing the failure rate of Ni-Ti files (Berutti et al., 2004). Moreover, irrigating solutions, 2.5% NaOCl and 17% EDTA, were used for antimicrobial activity (Siqueira et al., 2007), smear layer removal, respectively (Torabinejad et al., 2002). Their combination was associated with root canal cleanliness when done with manual agitation (Caron et al., 2010).

Results of the baseline data (age, gender and tooth type) is the same as a study by (Shabbir et al., 2021), which showed no statistically significant difference assuring similar distribution and avoiding the influence of confounding factors as well as all participants recording no pre-operative pain.

The results showed no significant difference in incidence of post-operative pain between both groups at all time intervals, similar to the study by (Shabbir et al., 2020). Thus, the null hypothesis was accepted and suggests the possible use of either medicaments.

Both groups recorded a non-significant gradual decrease in post-operative pain intensity through all time intervals. For $Ca(OH)_2$, severe pain was recorded at 24 hrs and 48 hrs, which coincides with (Walton et al., 2003) in which 16% at 24 hours and 8% at 48 hours recorded significant pain, which could be attributed to the buffering capacity of dentine. *E. faecalis* and *C.*

albicans, are highly resistant to $Ca(OH)_2$, limiting its efficacy (Siqueira & Lopes, 1999; Waltimo et al., 1999) and antimicrobial activity when compared with other intracanal medicaments (Eswar et al., 2013; Sinha et al., 2013).

Regarding propolis, this non-significant gradual decrease in post-operative pain, especially at 7 days, might be due to the antimicrobial activity stated by several studies (Awawdeh et al., 2009; Kayaoglu et al., 2011; Madhubala et al., 2011), in which propolis was proven to be more effective against resistant microorganisms than $Ca(OH)_2$. Furthermore, $Ca(OH)_2$ was reported to be potentially more toxic than propolis to both pulpal and periapical tissues (Al-shaher et al., 2004; Zare Jahromi et al., 2014).

The present study recorded that 7 (15%) out of the total 46 participants (5 propolis and 2 $Ca(OH)_2$) had severe pain with swelling requiring an emergency visit, comparable to the study by (Shabbir et al., 2020) that recorded 10 (14.8%) out of the total 68 participants (4 $Ca(OH)_2$ and 6 propolis). This is also lower than the study by (Ehrmann et al., 2007) which recorded only 2 out of 13 participants (15.38%) of $Ca(OH)_2$ had flare-up.

The cause of flare-up might be due to apical periodontitis when an imbalance between infectious microflora and the defensive mechanisms of the immune system occurred. Furthermore, during the chemo-mechanical preparation of the root canal, extrusion of infected debris from apical foramen to periradicular tissues might have increased inflammation (Siqueira, 2003; Siqueira & Barnett, 2004). Its intensity depends on the virulence of microorganisms and their amount in the periodontal tissues (Siqueira, 2003). Results are in accordance with *Genet et al* (Genet et al., 1987) who reported a flare-up rate of 27% in all endodontic cases treated. They also found a positive correlation between the incidence of pre-operative pain and the occurrence of post-operative pain. This finding might explain the lower rate of flare-up in the current study, as the cases included in this study were all the asymptomatic teeth.

A possible limitation of this study is the absence of a no treatment group, without intracanal medication, to establish a conclusive result on the importance of presence or absence of intracanal medicaments.

Conclusion:

Within the conditions of this clinical trial, it could be concluded that both groups recorded a drop in post-operative pain score. The intracanal use of propolis was effective in decreasing post-operative pain and could be a good alternative to calcium hydroxide, without its drawbacks. Future trials should be conducted on a bigger scale for testing propolis as an intracanal medicament.

Conflict of interest:

No conflict of interest.

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Ethics:

This study protocol was approved by the Research Ethics Committee, Faculty of Dentistry, Cairo University. Number: 8.9.15 and dated 30/9/2015.

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