

ORIGINAL ARTICLE

Assessment of factors influencing post-operative pain: the impact of smoking habit in root canal treatments obturated with carrier-based technique and epoxy resin sealer

ABSTRACT

Aim: To confirm predictive factors of post-operative pain (PP) and to further explore if smoking habit may influence the incidence, intensity and evolution of PP.

Methodology: Two hundred forty-five consecutive patients requiring endodontic treatment were included and pre-operative, patient and tooth-related factors were recorded. Patients were divided in 3 categories depending on smoking habit: non-smokers/light-smokers (<10 cigarettes/day)/heavy-smokers (≥ 10 cigarettes/day). Questionnaires recorded presence and intensity of post-instrumentation (PIP) and post-obturation pain (POP) in a 100 mm Visual Analogue Scale (VAS) at 24, 48, 72 hours (h), 7 days (d). Linear regression analysis determined the patient-, tooth- and treatment-related factors influencing intensity of PIP and POP at 24, 48, 72h, 7d after treatment. Logistic regression was used to assess variables influencing incidence of PP and need of painkillers. Linear-by-linear association test was used to assess differences in trend of intensity of PP among non-, light- and heavy-smokers at different time points.

Results: Two hundred twenty-three patients returned the questionnaires. Incidence and intensity of POP were influenced by: patient-related (smoking habit, gender), tooth-related (endodontic status, size of periapical lesions), treatment-related factors (obturation quality). Heavy-smokers showed significantly higher incidence of POP ($p < 0.03$) both 24 and 48h after treatment (OR=4.33, 95% CI 1.13-16.58 and OR=6.22, 95% CI 1.14-27.36 respectively). Different factors affected incidence and intensity of PIP/POP. Heavy-smokers had a higher incidence of PP than light and non-smokers. Smoking habit influenced intensity of POP during the first 48h after treatment.

Conclusions: Heavy smoking habit can adversely influence the intensity of post-obturation pain during the first hours after root canal treatment.

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Introduction

In Endodontics, the onset of pain and/or swelling after root canal treatment can be very distressing to both the patient and the operator, especially since patients often consider post-operative pain and flare-up as a benchmark to measure the clinician's skills (1). Post-operative pain is acquiring significance as a fundamental patient-centred outcome affecting quality of life and for this reason, the development of standard guidelines is advocated (2) to provide evidence-based recommendations. Post-operative pain of mild intensity is a common consequence of root canal preparation with a prevalence ranging from 3%-58%, while severe sequelae are rare but represent an emergency (1). The aetiology of PP is commonly related to tissues injury of chemical, mechanical or microbiological nature, most commonly due to the apical extrusion of infected debris and irritants (3). This fall-out is caused by many factors related to the experience of the operators and the instruments or techniques utilized, but factors inherent to patients also play an important role on PP occurrence and intensity. In any case, this post-preparation aftermath continues to show a high variability in prevalence among the increasing number of studies published by researchers. This variability can be due to the heterogeneity of inclusion criteria, study methods and intensity of pain taken in consideration.

Smoking behaviour is a multifactorial trait influenced by genetic and environmental components (4), primarily maintained by the positive and negative reinforcing properties of nicotine. It is demonstrated to cause a variety of diseases that can also lead to premature death and a significant reduction in the quality of life. While smoking habit is well known to adversely impact on oral health, by increasing the risk of oral cancer, lesions of the oral mucosa and periodontal disease, its role in endodontics is rarely considered. An association between prevalence of periapical periodontitis and smoking has been hypothesized with controversial

conclusions (5, 6) and for this reason clinical studies including an evaluation of smoking habit of the patients are advocated to address this gap in knowledge. To the best of our knowledge, this is the first study to evaluate the influence of smoking habit on the incidence, intensity and evolution of post-operative pain during the week after root canal treatment.

Therefore, the purpose of this prospective clinical study was to evaluate the prevalence of PP following RCT performed by postgraduate master's students in a University Endodontic Department, and to examine whether the smoking habit could be a risk factor contributing to a high recurrence rate of post-operative pain after endodontic treatment.

Material and Methods

This prospective study was conducted with the approval of the Ethical Committee of the University of Bologna (protocol number 0069637). Two hundred and forty-five consecutive subjects with single- or multi-rooted teeth requiring root-canal treatment for prosthetic reasons, irreversible pulpitis, pulp necrosis or failed primary treatment were enrolled in the study and treated between January and October 2018 in full compliance with the World Medical Association Declaration of Helsinki (7).

Sample size calculation was performed using the information derived from a preliminary trial comparing the incidence of post-obturation pain after 24 hours between smoker and non-smoker patients submitted to root canal treatments. Considering a size ratio of 0.3 between smokers and non-smokers, a minimum sample size of 145 non-smoker and 43 smoker subjects was required to detect differences accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test. Further estimations, anticipating 30% dropouts, suggested a total adjusted sample size of 244.4 patients.

Only those subjects having satisfied the following criteria were included in the study: the subject residing in the country, being 18-70 years old at time of treatment, systemically, healthy, having adequate oral hygiene with Plaque Index $\leq 20\%$ and the

tooth having pre-operative probing depth of ≤ 5 mm.

Subjects with the following criteria were excluded from the study: pregnancy, history of medication for chronic pain or with compromised immune response, failure to obtain authorization from patients, presence of difficult root canal anatomy (root canals with extreme curvatures, internal or external resorption or radiographically untraceable canal paths), or any accident or complication occurring during treatment. Patients whose forms were incompletely or inadequately filled out were excluded also.

A preliminary visit was performed to collect clinical and radiological findings. Each involved patient signed an informed consent and accepted to participate to the study. The enrolled clinicians were postgraduates ($n=17$), operating under the supervision of trained tutors. The same treatment protocol was followed. Demographic and medical information were registered for each patient, pre- and intra-operative data were recorded by a single operator. Among the variables registered, patients were inquired about their smoking habit and number of cigarettes consumed *per day*. Patients were then classified as non-, light- or heavy-smokers depending on the number of cigarettes consumed per day. Non-smokers were defined as subjects who had never smoked at least one cigarette every one to three days, light-smokers were defined as subjects who smoked <10 cigarettes every day in the past year and heavy-smokers were defined as subjects who smoked ≥ 10 cigarettes every day in the past year.

Type and location of treated teeth was also registered. Ethyl chloride (Crio Spray SZ, Karl San Marino) was used to test pulp vitality. In case of negative response, the diagnosis of necrosis was confirmed by the absence of bleeding after opening the pulp chamber. The patient was inquired about the presence of pre-operative pain in the previous 24 hours and pre-operative drug intake. The presence of periapical lesion was assured by the value of Peri-Apical Index (PAI) determined by 2 blinded experienced evaluators following Ørstavik et al. (8) directives and the diameter of the lesion was measured with a calliper. The curvature

Radius was also registered, and teeth were classified in 3 groups (straight, moderate or severe).

The RCT was performed using the following protocol: the patient was asked to rinse his mouth with 0.2% chlorhexidine for 60 seconds. Hard and soft tissues were then anesthetised based on the tooth location using mepivacaine (Carboplyina, Molteni, Scandicci, Italy). Rubber dam (Hygenic Dental Dam, Coltène Waledent, Cuyahoga Falls, OH, USA) was applied to isolate the operating field. A high-speed, water-cooled diamond bur (Intensiv, Grancia, Switzerland) was used to gain straight access to the pulp chamber. The interferences were removed using Batt and Gates-Glidden burs (Dentsply Sirona, Ballaigues, Switzerland). A 10 K-file (Dentsply Sirona) was then utilized to scout the root canal and negotiate to the apex. Working Length (WL) was determined using an apex locator (Root ZX, J Morita, USA) and confirmed by an intraoperative radiograph. A manual glide path was then achieved using K-files up to a nominal size #20. Root canal preparation was performed with Hyflex NiTi rotary instruments following manufacturer directions for use (500 rpm rotational speed, 2.5 Ncm torque). Irrigation was performed with 5 to 10 mL of 5% NaOCl solution (Nicolor 5, Ognà, Muggiò, Italy) and 1 to 3 mL of 10% EDTA (Tubuliclean, Ognà).

In retreatment cases, removal of previous obturation material was accomplished with size 4-3-2 Gates-Glidden drills and hand files with the use of solvent (Endosolv Septodont, Saint-Maur-des-Fosses Cedex, France). Final preparation was completed as previously described with Hyflex instruments.

A temporary filling with cotton pellets and Coltosol (Coltène-Whaledent, Altstätten, Switzerland) was applied after complete root canal preparation. The presence of occlusal and interproximal contacts was recorded. The patient was then dismissed after receiving post-operative instructions and a first questionnaire to register post-instrumentation pain (PIP) based on a printed Visual Analogue Scale (VAS) (9). Patients were asked to place a mark on the 10-cm line to evaluate the PP severity at 24, 48, 72 hours and 7 days after treatment as described in



a previous study (10). They were also asked to register analgesic intake over time. The results were collected in the second appointment and the treatment obturation of the root canal system completed with AH Plus sealer (Dentsply-DeTrey, Konstanz, Germany) and carrier-based system Thermanafil. The patient then received a second questionnaire to register post-obturation pain (POP), to be returned at the next appointment for final restoration.

Hence, intensity of post-operative pain was registered both after instrumentation and obturation appointments using a visual analogue scale (VAS) at 6, 12, 24, 48 h and 7 days after treatment, as well as the need of analgesic intake over time. General pain levels were also recorded as None (0), Mild (1-3), Moderate (4-6) and Severe (7-10), as previously reported (11).

Statistical analysis

A multivariate statistical analysis was used to control any possible confounding factor. A linear regression analysis was used to determine the patient-, tooth- and treatment-related factors that influenced the intensity of post-instrumentation (PIP) and post-obturation pain (POP) 24, 48, 72 hours and 7 days after treatment. A logistic regression was also used to assess the variables that influenced the incidence of post-operative pain and the need of pain-killers after both appointments. Odds ratios and their 95% CI were also estimated in the logistic regression analysis to measure the magnitude of the effect and quantify the strength of the association between the significant factors and the event. Beta coefficients and their 95% CI were also calculated in the linear regression models. The linear-by-linear association test was used to assess any difference in the trend of general levels of post-operative pain among non-, light- and heavy-smokers at the different time points.

Results

A total of 223 participants returned the questionnaires properly filled and were included in the statistical analysis. Out of these, 57% were females and 43% males

with 18% aged <30 years, 36% 30-50 years and 46% >50 years. Fifty-seven % of them presented pre-operative pain and 43% (49/223) did not. 70% were non-smokers and 30% smokers (156/67). From the smokers, 50.75% were considered light-smokers and 49.25% heavy-smokers.

Different factors affected the incidence and intensity of PIP and POP pain at the different time points.

The endodontic status of teeth influenced both the incidence of PIP 24h and 72h after treatment ($p < 0.05$). Patients presenting for a root canal treatment in a vital tooth experienced a significantly higher incidence of PP with an OR=3.96 (95% CI 1.16-13.47) and OR=8.56 (95% CI 1.1-62.2) respectively 24 and 72 hours after treatment. Also, patients with vital teeth showed a significantly higher intensity of PIP (beta coefficient= 1.38; 95% CI 0.24–2.53). No other factors significantly increased the chances of suffering PIP or the intensity at any time point after treatment. On the contrary, both the incidence and intensity of POP were influenced by many factors. Specifically, patient-related factors like smoking habit and gender significantly influenced the chances of experiencing POP during the first days after treatment. Heavy smokers showed a significantly higher incidence of POP ($p < 0.03$) both 24 and 48h after treatment with an OR=4.33 (95% CI 1.13-16.58) and OR=6.22 (95% CI 1.14-27.36), respectively. At the same time, the incidence of POP was also higher in women ($p = 0.017$) 24 and 72h after treatment with an OR= 2.45 (95% CI 1.18-5.1) and OR= 2.92 (95% CI 1.1-7.71), respectively. Obturation quality greatly affected the chances of suffering POP 24h after treatment ($p = 4 \cdot 10^{-4}$). Unintentional canal overfilling was associated to higher incidence of POP 24h with an OR= 10.1 (95% CI 3.37-30.23). Endodontic status and the size of periapical lesions also significantly affected the presence of POP 48h after treatment. Patients presenting for a root canal treatment in a vital tooth or in a tooth with a large lesion experienced a significantly higher incidence of POP with an OR= 5.36 (95% CI 1.02-28.18) for vital teeth and OR= 4.7 (95% CI 1.18-18.79) for large lesions.

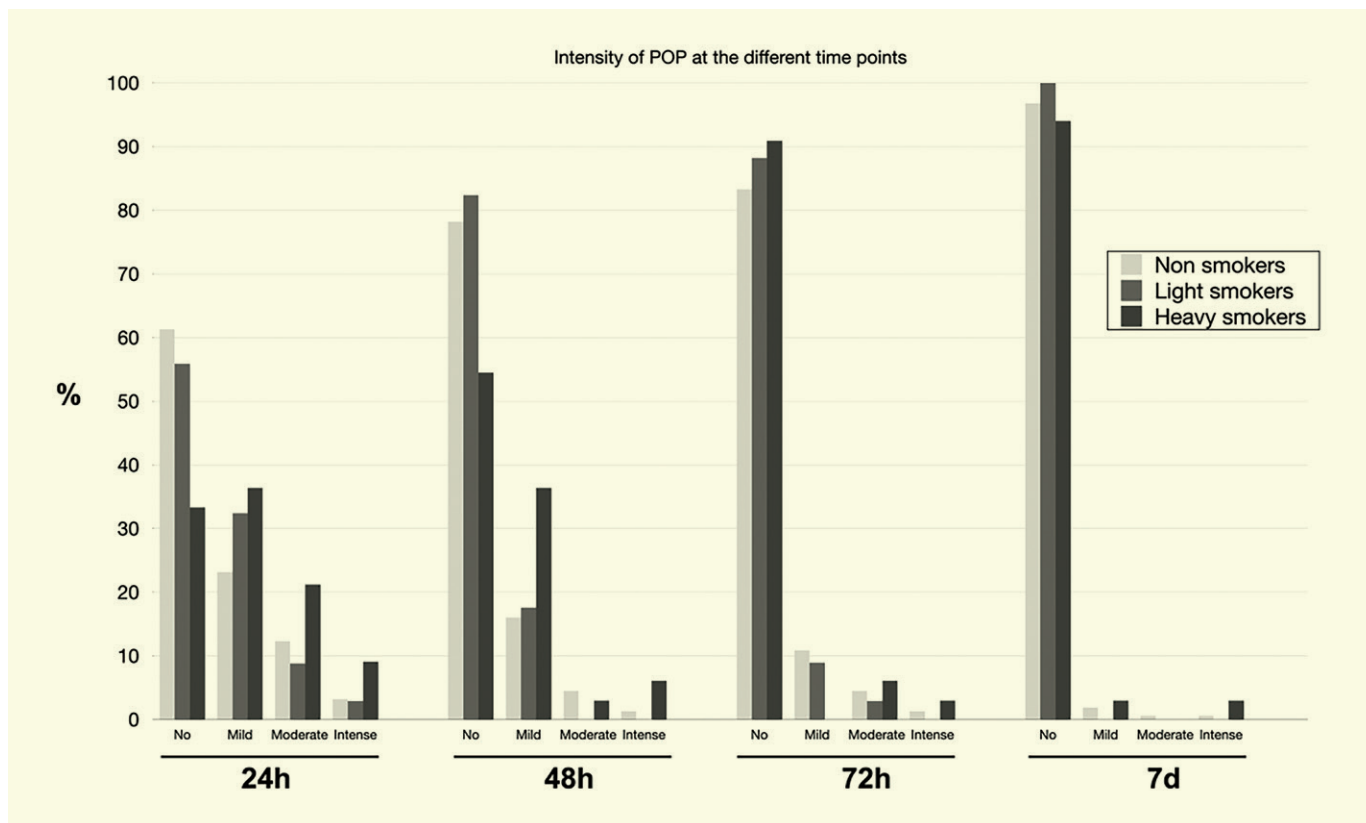


Figure 1. Intensity of post-obturation pain (POP) at different time points evaluated depending on smoking habit of patients is represented.

In terms of intensity, gender significantly influenced the intensity of POP at all different time points, and both the smoke habit and the size of the periapical lesion did at 24, 48 h after treatment. The presence of unintentional root canal overfilling and the endodontic status also affected the intensity of pain 24h after treatment significantly. Endodontic status and the size of the periapical lesion also influenced the need for medication intake.

Table 1 shows the percentage of participants suffering post-operative pain, as well as mean (and SD) VAS score, at the different time points related to smoking habit. Heavy smokers showed a significant tendency for a higher general intensity of PIP 48 hours ($p=0.03$) and POP 24 ($p=0.006$) and 48 h after treatment ($p=0.02$) than light or non-smokers (Fig. 1).

Discussion

Post-operative pain is one of the most relevant factors that impacts on the patient psychology and tolerance (12). This study

was designed to assess those factors influencing post-operative pain after root canal treatments performed in a University Department and, more specifically, to better understand the influence of smoking habits in the incidence, intensity and evolution of post-operative pain in endodontics.

Post-operative pain management is very important in endodontic practice because it joins both patients and clinicians in an unpleasant experience. Thus, its prevention and management are of prime importance (13). Several strategies have been used to evaluate post-operative pain and in the present research the VAS scale was chosen because it has been well validated and extensively used by researchers as a standard outcome (9, 11, 14, 15). Many variables influence the occurrence of post-operative pain and for this reason it is challenging to single out possible causes. In the present study all the included teeth were instrumented with thermally-treated HyFlex NiTi files to avoid variables related to instrumentation. Recently,



Table 1
Descriptive analysis of pre-operative and post-operative variables.

Pre-operative Variables	(N)
Tooth Arch	
Maxilla	126
Mandible	97
Teeth group	
Incisive	30
Canine	7
Premolar	66
Molar	120
Initial PAI	
PAI ≤ 2	135
PAI ≥ 3	88
Initial diagnosis	
Pulp exposure	38
Irreversible pulpitis	60
Acute AP	28
Chronic AP	72
Prosthetic reason	25
Post-operative Variables	
Root filling quality	
Underfilled	5
Adequate	184
Overfilling	34
Apical Diameter	
<35	148
35-45	66
≥ 50	9
Curvature radius	
Staight	108
Moderate	94
Severe	1
Final coronal restoration	
Composite	105
Post	93
Crown	25
Total	223

it was reported a lower intensity of PP when retreatment procedures were performed with continuous rotation instead of reciprocation (16). Interestingly, in the current study the incidence of PIP after treatment of teeth with vital pulp was higher, as previously reported (17). It remains fascinating to further investigate the role of extrusion beyond the apex during instrumentation and to correlate the operator-dependent variables. Only teeth treated in

multiple visits were herein included to avoid the confounding factors associated with instrumentation and obturation in single visit.

The present study confirmed the influence of several factors in POP pain phenomena. A relation between patient-related factors like gender and incidence of POP was confirmed, observing that female patients experienced a higher level of pain in the short term, as previously reported (18-20). The size of periapical lesion and the endodontic status (vital pulp) also influenced the presence of POP, in accordance with previous findings (21, 22) even if implications are controversial (18). Hence, the increase of pain intensity associated with large periapical lesion and with vital teeth influenced the need for medication intake. The available clinical evidence suggests that the obturation technique with more recent calcium-silicate based sealers provided similar clinical and radiographic results when compared to alternative obturation materials and techniques (23, 24). It remains inconclusive whether premixed bioceramic sealers differ from epoxy resin-based sealers in terms of post-operative pain (24). Moreover, epoxy resin-based sealers are considered a reference material and have been described as the gold standard for sealer cements (25-26). Resin based sealer extrusion does not seem to impair endodontic outcomes, neither in the medium nor in the long term, as previously pointed out (27-30). However, similar to the findings by a prior study (20), an unintentional overfilling of sealer was confirmed to increase the post-operative pain levels and should be therefore carefully avoided during clinical procedures of root canal obturation with carrier-based systems and resin-based sealers.

Increasing attention is given to the role of smoking habit as a risk factor for chronic pain due to the profound changes produced in human physiology (31). Smoking may increase pain sensitivity in general by impairing the delivery of oxygen-rich blood to bones and tissues. Decreasing blood and nutrient flow can cause tissue degeneration. Physicians also link smoking with fatigue and slower healing, factors that make

Table 2

Percentage of participants suffering post instrumentation pain (PIP), and post obturation pain (POP) as well as mean (and standard deviation (SD)) visual analogue score (VAS), at the different time points related to smoking habit.

	Mean VAS (SD) / Percentage of participants suffering PP							
	PIP				POP			
	24h	48h	72h	7d	24h	48h	72h	7d
Non smokers	1.92 (2.3) / 46.8	1.2 (1.9) / 27.6	0.69 (1.4) / 17.3	0.26 (0.9) / 5.1	1.55 (2.1) / 38.7	0.84 (1.5) / 21.8	0.64 (1.3) / 16.7	0.2 (0.7) / 3.1
Light smokers	1.72 (1.6) / 52.9	1.1 (1.5) / 29.4	0.53 (0.9) / 11.8	0.12 (0.5) / 2.9	1.59 (2) / 38.7	0.64 (1) / 17.6	0.52 (1.2) / 11.8	0.03 (0.1) / 0
Heavy smokers	2.73 (2.4) / 63.6	1.74 (2.1) / 48.5	0.8 (1.9) / 12.1	0.41 (1.5) / 9.1	2.78 (2.6) / 66.7	1.55 (1.9) / 45.5	0.83 (1.7) / 9.1	0.35 (1.5) / 6

painful conditions more prominent (31). Regarding pulp tissue, a significant increase of levels of neuropeptides such as calcitonin-gene related-peptide (CRGP) has been documented in the pulps from painful teeth of smokers compared with non-smokers (32). Moreover, smokers have a significantly reduced expression of TNF- α , and hBD-2 levels compared with non-smokers, suggesting that dental pulp of smokers possesses limited defence mechanisms against microorganisms (33). Smoking appears to be one of the most significant prognostic factors in the progression of marginal periodontitis (34) and has been previously reported as a statistically significant risk factor for developing apical periodontitis (35). Moreover, despite the paucity of evidence connecting smoking with endodontic disease, a significant association was found between this habit and a reduced chance of periapical bone healing (6, 34, 36, 37). This speculation has also been confirmed by a recent study (38) that found smoking as a significant predictive factor for a worse outcome in endodontics. Even if limitations of the analysis of this research include possible bias, due to the subjectivity of pain perception and to the smaller ratio of smoker patients, an interesting association between smoking habit and post-operative pain intensity was found, identifying smoking as a relevant predictor of pain. Evidence of change in the microbiome of

smokers has been also reported (39), potentially leading to shifts in functional pathways with implications for smoking-related diseases. It can be speculated that heavy smokers could have a more aggressive pathogenic bacterial flora and therefore experiencing more PP despite the same extrusion of debris from the apex during endodontic procedures. Although no previous studies commented the relation between smoke factor and post-operative pain, it may be hypothesized from our results that smoking habit plays an important role in the process of pulpal/periapical inflammation and pain, by inducing an increase of perceived pain intensity. These considerations must be confirmed by increasing the number of analysed patients and further investigations on the role of tobacco use on endodontic pain are required.

It might be appropriate for the clinicians to inform a smoking patient that a particular recommendation related to the incidence and resulting management of post-endodontic pain might be applicable, after considering all other circumstances pertinent to that individual.

Conclusions

Within the limitations of this prospective study, present findings suggest a higher incidence of PP associated to heavy smokers, in female patients, after



unintentional overfilling, depending on the periapical lesion size and on the pre-operative pulpal status. There is a need for clinical pain researchers to fulfil these requirements in future trials in order to optimize post-operative pain management recommendations.

Clinical Relevance

Heavy smoking habit can adversely influence the intensity of post-obturation pain during the first hours after root canal treatment.

Conflict of Interest

All authors disclose any potential sources of conflict of interest.

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Ethical approval

All procedures performed in the present study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Compliance with Ethical Standards

Chiara Pirani declares that she has no conflict of interest. Francesco Iacono declares that he has no conflict of interest. Carlo Prati declares that he has no conflict of interest. Ana Arias declares that she has no conflict of interest.

References

- 1 Sathorn C, Parashos P, Messer H. The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: a systematic review. *Int Endod J.* 2008; 41, 91-9.
- 2 Nosrat A, Dianat O, Verma P, Nixdorf DR, Law AS. Postoperative Pain: An Analysis on Evolution of Research in Half-Century. *J Endod.* 2021; 47, 358-65.
- 3 Siqueira JF Jr. Microbial causes of endodontic flare-ups. *Int Endod J.* 2003; 36, 453-63.
- 4 West R. Tobacco smoking: Health impact, prevalence, correlates and interventions. *Psychol Health.* 2017; 32, 1018-36.
- 5 Rodriguez FR, Taner B, Weiger R, Walter C. Is smoking a predictor of apical periodontitis? *Clin Oral Investig.* 2013; 17, 1947-55.
- 6 Aminoshariae A, Kulild J, Gutmann J. The association between smoking and periapical periodontitis: a systematic review. *Clin Oral Investig.* 2020; 24, 533-45.
- 7 World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *JAMA.* 2020; 284, 3043-5.
- 8 Ørstavik D, Kerekes K, Eriksen HM. The periapical index: A scoring system for radiographic assessment of apical periodontitis. *Endod Dent Traumatol.* 1986; 2, 20-34.
- 9 Bodian CA, Freedman G, Hossain S, Eisenkraft JB, Beilin Y. The Visual Analog Scale for Pain: Clinical Significance in Postoperative Patients. *Anesthesiology.* 2001; 95, 1356-61.
- 10 Erdem Hepsenoglu Y, Eyuboglu TF, Özcan M. Postoperative Pain Intensity after Single- versus Two-visit Nonsurgical Endodontic Retreatment: A Randomized Clinical Trial. *J Endod.* 2018; 44, 1339-46.
- 11 Emara RS, Abou El Nasr HM, El Boghdadi RM. Evaluation of postoperative pain intensity following occlusal reduction in teeth associated with symptomatic irreversible pulpitis and symptomatic apical periodontitis: a randomized clinical study. *Int Endod J.* 2019; 52, 288-96.
- 12 Abdulrab S, Rodrigues JC, Al-Maweri SA, Halboub E, Alqutaibi AY, Alhadainy H. Effect of Apical Patency on Postoperative Pain: A Meta-analysis. *J Endod.* 2018; 44, 1467-1473.
- 13 Elkhadem A, Ezzat K, Ramadan M, et al. The effect of preoperative oral administration of prednisolone on postoperative pain in patients with symptomatic irreversible pulpitis: a single-centre randomized controlled trial. *Int Endod J.* 2018;51:e189-96.
- 14 Adigüzel M, Yılmaz K, Tüfenkçi P. Comparison of postoperative pain intensity after using reciprocating and continuous rotary glide path systems: a randomized clinical trial. *Restor Dent Endod.* 2019; 44, e9.
- 15 Aslan T, Dönmez Özkan H. The effect of two calcium silicate-based and one epoxy resin-based root canal sealer on postoperative pain: a randomized controlled trial. *Int Endod J.* 2021; 54, 190-7.
- 16 Bürklein S, Arias A. Effectiveness of root canal instrumentation for the treatment of apical periodontitis: A systematic review and meta-analysis. *Int Endod J.* 2023 Oct;56 Suppl 3:395-421. doi: 10.1111/iej.13782. Epub 2022 Jun 23. PMID: 35670625.
- 17 Gotler M, Bar-Gil B, Ashkenazi M. Postoperative pain after root canal treatment: a prospective cohort study. *Int J Dent.* 2012; 5, 310467.
- 18 Ng YL, Glennon JP, Setchell DJ, Gulabivala K. Preva-

- lence of and factors affecting post-obturation pain in patients undergoing root canal treatment. *Int Endod J.* 2004; 37, 381-91.
- 19 Arias A, de la Macorra JC, Azabal M, Hidalgo JJ, Peters OA. Prospective case controlled clinical study of post-endodontic pain after rotary root canal preparation performed by a single operator. *J Dent.* 2015; 43, 389-95.
 - 20 Yu YH, Kushnir L, Kohli M, Karabucak, B. Comparing the incidence of postoperative pain after root canal filling with warm vertical obturation with resin-based sealer and sealer-based obturation with calcium silicate-based sealer: a prospective clinical trial. *Clin Oral Investig.* 2021; 25, 5033-42.
 - 21 Siqueira JF Jr, Rôças IN, Favieri A et al. Incidence of postoperative pain after intracanal procedures based on an antimicrobial strategy. *J Endod* 2002; 28, 457-60
 - 22 Tan HSG, Lim, KC, Lui JN, Lai WMC, Yu VSH. Postobturation Pain Associated with Tricalcium Silicate and Resin-based Sealer Techniques: A Randomized Clinical Trial. *J Endod.* 2021; 47, 169-177.
 - 23 Sabeti MA, Karimpourtalebi N, Shahravan A, Dianat O. Clinical and Radiographic Failure of Nonsurgical Endodontic Treatment and Retreatment Using Single-cone Technique With Calcium Silicate-based Sealers: A Systematic Review and Meta-analysis. *J Endod.* 2024 Jun;50(6):735-746.e1. doi: 10.1016/j.joen.2024.03.007.
 - 24 Zamparini F, Lenzi J, Duncan HF, Spinelli A, Gandolfi MG, Prati C. The efficacy of premixed bioceramic sealers versus standard sealers on root canal treatment outcome, extrusion rate and post-obturation pain: A systematic review and meta-analysis. *Int Endod J.* 2024 Apr 12. doi: 10.1111/iej.14069.
 - 25 Viapiana R, Moinzadeh AT, Camilleri L, Wesselink PR, Tanomaru Filho M, Camilleri J. Porosity and sealing ability of root fillings with gutta-percha and BioRoot RCS or AH Plus sealers. Evaluation by three ex vivo methods. *Int Endod J.* 2016 Aug;49(8):774-82. doi: 10.1111/iej.12513.
 - 26 Pirani C, Camilleri J. Effectiveness of root canal filling materials and techniques for treatment of apical periodontitis: A systematic review. *Int Endod J.* 2023 Oct;56 Suppl 3:436-454. doi: 10.1111/iej.13787.
 - 27 Ricucci D, Rôças I N, Alves FR, Loghin S, Siqueira JF Jr. Apically Extruded Sealers: Fate and Influence on Treatment Outcome. *J Endod.* 2016; 42, 243-9.
 - 28 Pirani C, Zamparini F, Peters OA et al. The fate of root canals obturated with Thermafil: 10-year data for patients treated in a master's program. *Clin Oral Investig.* 2019; 23, 3367-77.
 - 29 Goldberg F, Cantarini C, Alfie D, Macchi RL, Arias A. Relationship between unintentional canal overfilling and the long-term outcome of primary root canal treatments and nonsurgical retreatments: a retrospective radiographic assessment. *Int Endod J.* 2020; 53, 19-26.
 - 30 Atav Ates A, Dumani A, Yoldas O, Unal I. Post-obturation pain following the use of carrier-based system with AH Plus or iRoot SP sealers: a randomized controlled clinical trial. *Clin Oral Investig.* 2019 Jul;23(7):3053-3061. doi: 10.1007/s00784-018-2721-6.
 - 31 Shi Y, Weingarten TN, Mantilla CB, Hooten WM, Warner DO. Smoking and Pain. *Pathophysiology and Clinical Implications.* *Anesthesiology.* 2010; 113, 977-92.
 - 32 Awawdeh L, Lundy FT, Shaw C, Lamey PJ, Linden GJ, Kennedy JG. Quantitative analysis of substance P, neurokinin A and calcitonin-gene related peptide in pulp tissue from painful and healthy human teeth. *Int Endod J.* 2002; 35, 30-6.
 - 33 Ghattas Ayoub C, Aminoshariae A, Bakkar M et al. Comparison of IL-1 β , TNF- α , hBD-2, and hBD-3 Expression in the Dental Pulp of Smokers Versus Nonsmokers. *J Endod.* 2017; 43, 2009-13.
 - 34 Duncan HF, Pitt Ford R. The potential association between smoking and endodontic disease. *Int Endod J.* 2006; 39, 843-54.
 - 35 Kirkevang LL, Wenzel A. Risk indicators for apical periodontitis. *Community Dent Oral Epidemiol.* 2006; 31, 59-67.
 - 36 Walter C, Rodriguez FR, Taner B, Hecker H, Weiger R. Association of tobacco use and periapical pathosis-a systematic review. *Int Endod J.* 2012; 45, 1065-73.
 - 37 Pirani C, Iacono F, Gatto MR, et al. Outcome of secondary root canal treatment filled with Thermafil: a 5-year follow-up of retrospective cohort study. *Clin Oral Investig.* 2018; 22, 1363-73.
 - 38 Kirkevang LL, Ørstavik D, Bahrami G, Wenzel A, Vaeth M. Prediction of periapical status and tooth extraction. *Int Endod J.* 2017; 50, 5-14.
 - 39 Wu J, Peters BA, Dominianni C, et al. Cigarette smoking and the oral microbiome in a large study of American adults. *ISME J.* 2016;10, 2435-46.