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Cumulative Factors Determining Endodontic Operative Pain and Persistent Apical Periodontitis Following Nonsurgical Root Canal Treatment in Permanent Teeth - A Comprehensive Literature Review

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Abstract **Review Article**

Pain and discomfort experienced during and after endodontic treatment are referred to as endodontic operative pain. The condition is complicated and multifactorial, with **preoperative** factors relating to the host and the affected tooth, **intra-operative** factors resulting from mechanical, chemical, or microbial damage to peri-radicular tissues, and **postoperative** factors (the success of the root canal treatment, the effectiveness of pain management techniques and the persistence of periapical inflammation). The presence of persistent apical periodontitis after unsuccessful non-surgical root canal treatment may need endodontic apical surgery. This comprehensive literature review aims to explore the etiopathogenesis of endodontic operative pain and identify the factors that can influence and aggravate it. By understanding the underlying mechanisms and potential influences, dentists can implement effective strategies to prevent or manage endodontic operative pain more efficiently. Dental practitioners must convey to the patients regarding the root canal treatment process, potential discomfort and available pain management options clearly, alleviating patients' fears and enhancing their compliance with postoperative care instructions.

Keywords: Endodontic pain, root canal treatment, Endodontic operative pain, etiopathogenesis factors, post-operative pain, apical periodontitis, review

INTRODUCTION

The basic objective of root canal treatment is to remove irritants from the root canal, thereby allowing for the healing of periapical tissues. This is followed by 3dimensional obturation of the root canal system and proper coronal sealing to prevent re-infection of the canal. The ultimate goal is to preserve the natural set of teeth and ensure the tooth functions properly.

Endodontic operative pain is defined as any degree of pain either during root canal treatment or after obturation filling, which could also be influenced by pre-operative factors and is considered a concern for both patients and clinicians [1, 2]. It was found that between 3%- 58% of patients that underwent root canal treatment experienced operative pain [2-7]. A low incidence of endodontic operative complaints can be expected using current science-based treatments and well-founded biological principles.

Endodontic operative pain can be either immediate or persistent long-term [8,9,10]. Even when endodontic treatment has complied with the highest acceptable standards, early occurrence of minor transient operative pain is typical [10] due to the preparation of the root apical area, anesthetic injection, rubber dam clamp pressure and due to patient's mouth being open for an extended period of time [11]. Patients should anticipate this, and mild analgesics make it simple to manage [2]. However, endodontic operative pain can last past the mild stage due to other multifactorial causes and a potential pathogenic link to acute periapical inflammation [10,11]. This inflammation may be brought on by the host condition, the affected tooth, or secondary to chemical, mechanical, and/or microbial peri-radicular damage that can occur intraoperatively [5,10,11].

An important aspect of endodontic treatment is preventing and managing endodontic operative pain [6]. Preoperative pain management involves accurate

diagnosis and patient's anxiety reduction. The use of efficient local anesthetic and proper operative techniques greatly reduces intraoperative pain. Following treatment, mild-moderate postoperative pain can be managed through analgesics. Patients' tolerance for pain is increased and their attitude toward receiving further dental care is enhanced when they are informed previously about the typical endodontic operative pain.

Diagnosis and source of pain

The first phase of treating a dental patient with pain is of course diagnosis. The diagnosis of the pain is not simple for the patient that has recently had an endodontic procedure.

- Current pain symptoms may be due to another tooth, or post-injection sequelae. Or the original endodontic diagnosis may have been wrong [12] or pain is due to secondary iatrogenic causes in the root canal-treated tooth.

The first step in good endodontic pain management should be to fully understand the patient's primary complaint. The clinician's evaluation of the pain will be aided by information gathering, such as when the symptoms started, whether they are intermittent or continuous, if they are light, moderate or severe pain, whether there is an associated swelling and whether anything exacerbates or relieves the symptoms. The patient's medical and dental histories should be re-reviewed. The following clinical examinations should be performed: check for any discoloration, areas of swelling or ulceration, exudation, lost or damaged restorations, cracked or fractured teeth, any obvious changes in occlusal contact; need to perform axial and right-angle percussion, apical palpation, occlusal bite-stick test, thermal stimulation (cold and hot if indicated) and periodontal exploration. The dentist must decide if a more accurate angle dental x-ray can help explain the cause of the current pain. However, it can be difficult to explain the existence of bone lesions, especially in the initial stages. The results of these x-ray and clinical examinations may reveal other tooth-related symptoms, or they may be related to teeth that have recently undergone endodontic treatment, or they may not be due to tooth related at all (non-odontogenic) [13].

- It has also been demonstrated that several non-odontogenic ailments can mimic endodontic or odontogenic pain.

3.4% of patients in one study reported continued non-odontogenic discomfort after root canal treatment [14]. There are four potential pathways that can lead to non-dental discomfort in the alveolar region: (i) myofascial pain syndrome / musculoskeletal related problem (ii) neuropathic pain disorder (iii) headache conditions that present in the dentoalveolar region and (iv) medical pathological condition not directly related to the dentoalveolar area but causing referred pain there, such as sinus disease, salivary gland problems, brain tumors, angina, oropharyngeal cancer, and craniofacial vascular issues [15]. Patients undergoing endodontic treatment often present with preexisting inflammatory dentoalveolar pain, making it difficult to distinguish between patients with non-dental pain arising from underlying disease and those with procedural pain. Although cases of non-odontogenic referred pain, such as musculoskeletal disorders, medical pathological conditions and headache disorders do not appear to be adequately treated with endodontic treatment, it is thought that cases of neuropathic pain that is initially misdiagnosed will continue to hurt even after endodontic treatment [16] or become more stubborn (recalcitrant) [17].

- In the article by Ree [18], they describe the diagnosis and treatment of an unsuspected flare-up 1 week after root canal treatment and prosthodontic treatment. The swelling and pain were found to be associated with an accidentally embedded piece of impression material and had nothing to do with the root canal treatment procedure. Dentists should have the responsibility to evaluate patients with broad vision.

Incidence, Intensity, and Duration

Hayes and Patterson first introduced Visual Analogue Scales [19]. This is a valid and accurate method that is frequently used in the endodontics literature. It shows a continuous line with numbers to represent the severity of pain [20].

Patients noting 1 and 2 pain levels (weak pain in VAS Scale) are only experiencing "postoperative discomfort". In addition, the Hawthorne effect [21], that is, the change in the behavior of a subject because of the special attention and status received from participation in an investigation, can provoke patients to overestimate their pain levels.

Gotler et al [6] study showed a high incidence of pain after endodontic therapy, ranging from 34.6% to 63.8%, depending on the preoperative condition of the pulp. Also, pain shows a tendency to increase between 6 and 12 h after treatment, reaching a prevalence of about 40% in 24 h and falling to 11% one week after treatment [5]. Ali et al [7] reported an overall incidence of postoperative severe pain in root canal-treated teeth was 9% after 12 h, which was reduced to 8.6% after 24 h and drastically to 4% after 48 h. The pain was more frequent during the first 24 hr of the observation period and quickly decreased thereafter. Similar findings were also reported by Fox J et al [22] and Sameer et al [23].

The presence and duration of preoperative pain in the dental site lasting more than 3 months, a history of chronic pain or painful orofacial treatment, and female gender were among the many significant risks for pain persisting after successful endodontic treatment according to N Polycarpou et al [8] (Table 1, Table 2).

Gao et al., [24] study concluded that the back propagation artificial neural network model could be used to predict postoperative pain 95.6% accurately following endodontic treatment and showed clinical feasibility.

Table 1: Prevalence and Factors associated with Endodontic operative pain reported by different Studies

Author	Title	Incidence of pain	Age	Gender Female	Arch/ Tooth	Pulp status	Periapical lesion	Preoperative pain	No. of visit
Umut Aksoy *et al.*, [25] 2020	Monte Carlo simulation-systematic literature search			✓		✓ Necrotic	✓	✓	Multiple visit
N Polycarpou *et al.*, [8] 2005	Clinical Study	Persistent pain 12%		✓				✓	
Ali, Syed Gufran; Mulay *et al.* [7] 2012	Randomized Clinical trial	Pain at: 12Hr:9%, 24hr:8% 48hr: 4%	Older Patients had more pain	✓	Mandible	Pulp vitality was not a factor		✓	
A Arias *et al.*, [26] 2013	Prospective Clinical study		Older Patients had more pain	✓	Molars Mandible	✓	✓	✓	
J.J. Segura-Egea, R. Cisneros-Cabello [27]2009	Clinical study	54% had no pain	Younger Patients reported more pain	•	Posterior teeth Mandible	Irreversible pulpitis had more pain than necrotic	Acute apical periodontitis	✓	
Y-L Ng *et al.*, [4] 2004	Clinical study	40.2% of patients had pain in 48 h		✓	Molars		Less than 3 mm periapical lesion	✓	Single visit
Shresha *et al.*, [28] 2018	Clinical study	Pain at: 6hr:79.2% 72hr:22%		✓	Posterior teeth No of canals			✓	
J. M. Genet *et al.*, [29] 1987	Clinical study	27% of patients had post-operative pain		✓	No of canals	Non vital	Larger than 5mm periapical lesion	✓	
N. Imura *et al.*, [9] 1995	Clinical study	1.58 % of patients had flare-ups	•	•	•	Pain more in Retreatment cases	✓	✓	Multiple visit
Akram Alí *et al.*, [30] 2016	Clinical study	Mean 2-3 on the VAS scale		✓	Molars Mandible			✓	

- No significant effect

Table 2: Multifactorial Causes / Etiopathogenesis of Endodontic Operative Pain

PREOPERATIVE FACTORS			INTRAOPERATIVE FACTORS				POSTOPERATIVE FACTORS	
Host			Operator dependent Non-microbial		Microbial			
General	Tooth		Mechanical	Chemical -foreign body reaction	Primary/ Intra-radicular	Secondary/ Extra-radicular		Possible need for periapical surgery
	Anatomy	Pathology						
Age	Tooth Type - Anterior /Posterior No. of roots/ No. of canals	Pulpal status: vital /irreversible/ necrotic/ nonvital	•Poor case selection, incorrect diagnosis •Working with no Rubber Dam isolation	•amalgam/ restorative particles extrusion through periapex • Oral Pulse granuloma	Imbalance of root canal microbes - Incomplete residual necrotic pulp and bacterial debridement	Secondary microbial flora from the open cavity, fistula, periodontal pockets, through tooth fractures…	No coronal hermetic seal -leaky filling-poor coronal restorations	Persistent microbes in inaccessible apical third of complex root canal system/ severely extruded endodontic materials
Gender	Arch- Maxilla/ Mandible	Peri radicular diseases. Radiographic absence or presence of dental disease	No. of visits for completion (Single visit / Multiple visits)	Intracanal Irrigation usage and extrusion	Increased oxygen reduction potential	Extraradicular Exacerbating apical periodontitis lesions.	Hyper occlusion	True Cysts - Cystic apical periodontitis
Medical history - host immune response	•Unusual tooth anatomy/ anatomic variants •Apical Root Fenestration	Preoperative pain: severity, abscess, swelling. Tenderness to percussion/ palpation	Instrumentation Technique: •Access Cavity •Working Length •Crown down technique •Glide path, Apical patency •Rotary Niti endo files Vs hand SS files	Intracanal Medicament usage and extrusion	Apical extrusion of root canal bacteria-infected debris into periapex	Extraradicular Infected periapical pocket cysts	Role of analgesics and other medication in pain management	Endogenous Cholesterol crystals accumulation in periapex
Fear, Anxiety	Calcified canals/ altered canal spaces affect the ability to complete shaping & cleaning	Periodontal health of surrounding tissue (endo periodontal lesions)	Over instrumentation	Cellulose granuloma - paper points / Sterile and medicated cotton wool extrusion	Interradicular fungi, yeast	Extraradicular Periapical actinomycosis	Adjunctive therapy to reduce postop pain: •Lower Laser therapy •Cryotherapy •Phototherapy	
	Occlusal contact with the antagonist	Traumatic injuries, Tooth crack / Root Fracture/ Apical root resorption / Internal resorption	Recapitulation- Prevent Apical extrusion of dentinal debris	Intracanal Sealant usage and extrusion		Extraradicular Viruses		
	Misaligned teeth / Technical difficulties	Previously treated (primary RCT vs Re-RCT)	Procedural errors -negligence/ mechanical perforation/ ledges/ separated instruments / Missed canals/ untreated canal spaces/ underextended obturation.	Root canal Gutta-percha over extended filling				

PREOPERATIVE FACTORS: HOST

Age

The incidence of endodontic operative pain or flare-up or unhealed periapical lesion is found to be high among older patients 41-65 years old [7, 23,26, 31]. This may be because of less pain tolerance, less blood flow, and delayed healing [7, 26] in older patients. This could also be related to the changes in both humoral and cell-mediated immunity that occur naturally due to ageing [32]. Ozdemir et al [33] reported in their study that the action of sodium hypochlorite is affected by the increasing age of the patient, and they found it to be less effective in decreasing the count of Enterococcus faecalis in aged teeth.

J.J. Segura et al., [27] study reported that 60% of patients ageing 35 years and younger experienced some type of post-operative pain, whereas only 39% of patients older than 35 years felt pain. The narrowing of the diameter of the root canal in the teeth of older patients, leading to less debris extrusion and a weaker inflammatory response due to decreased blood flow, is one of the reasons discussed in endodontic literature for why older patients may experience less post-operative pain.

N. Imura et al. [9], El Mubarak et al. [34] studies reported that age had no significant effect on post-operative pain.

Effect of Gender

Women reported a higher mean pain intensity than men, 6 and 18 h post endodontic treatment [4,6,7, 8,25,26,28-31]. This could be explained by biological and physiological differences in how each gender responds to pain [4, 7, 35] or by males reporting less pain since it is assumed that they can tolerate it better than women [29].

Javier et al. [36] observed that men had much more post-operative discomfort and functional limitations than women after endodontic treatment.

No variations between males and females were observed in the category with the severe post-operative pain intensity, as reported by Elizabeth et al. [37], N. Imura et al. [9], and J. Segura et al. [27].

Systemic Diseases

Numerous systemic illnesses may affect local tissue resistance, impairing the bone's capacity for regenerative regeneration. These include osteoporosis, hyperthyroidism, hyperparathyroidism, and Paget's disease. Periapical healing is also impacted by additional factors such as nutrition, hormones, chronic illness, vitamins, stress, and dehydration [38]. Systemic disease may frequently require changing the course of treatment.

It was also noted that the flare-up rate after endodontic treatment procedures is low in patients using systemic steroids as treatment for systemic diseases. Steroids suppress the acute inflammatory response during the chemomechanical preparation of the root canal when mechanical, chemical, and/ or microbial factors irritate the apical periodontal tissue [39].

Kaur *et al.* [40], revealed that interappointment flare-ups in patients with Diabetes are higher than in patients without Diabetes, the same as observed by Sameer et al [23] and Armada Dias et al [41].

Elizabeth et al [37] found that a lower resting heart rate and lower diastolic arterial blood pressure correlated with higher mean Day 1 pain following endodontic treatment. Existing studies by W Maixner et al [42] and Fillingim et al [43] have already established that higher resting blood pressure is associated with reduced pain sensitivity. Research indicates that pain-free individuals with high blood pressure at rest tend to have higher pain thresholds and tolerances compared to those with low blood pressure [37]. One potential explanation for the influence of arterial blood pressure on experimental pain sensitivity involves the activation of the carotid sinus baroreceptors [44].

Fear, Anxiety

The patient's pain perception and reaction thresholds are influenced by fear of dental treatment, anxiety, apprehension and other psychological factors. Patients with dental phobias tend to be difficult, because of their low psychophysiological tolerance.

“Hot tooth” or occurrence of intra- operative pain during root canal treatment procedures has been associated with a higher pain intensity post-treatment due to the increased anxiety experience and reduced pain threshold for patients with inadequate anesthetic effect [45]. Lavanya et al [46] showed that if the patient required additional intraoperative anesthesia, the odds ratio for experiencing postoperative pain increased 4.8 and 5.8-fold, respectively 24 and 48 h after treatment. Moreover, preoperative pain still played a significant role seven days after treatment.

Patient-centered behavioral techniques can assist in coping with anxiety and tension during dental procedures. Dentists must be aware of the technique that fits each patient the best. Anxiety stimulates the patient’s nociceptors, causing genomic changes that negatively affect the healing mechanism [47]. Patients who received positive information about endodontic treatment reported less fear of the pain associated with the procedure. By adopting this approach, patients can experience greater comfort both before and during treatment, reducing avoidance behavior and enabling them to make treatment decisions based on rational considerations rather than fearful expectations [48].

Individuals classified as catastrophizers tend to magnify or exaggerate the threat or severity of pain.

Catastrophizing pain is a term that describes a sequence of exaggerated and lingering negative thoughts and emotions that happen when experiencing a painful stimulus, regardless of its nature or severity [49]. This could be the cause of reporting persistent pain. Patient optimism might reduce the feeling of persistent pain.

PREOPERATIVE FACTORS: TOOTH

Tooth type, Arch:

Gotler et al [6] report that there is no statistically significant correlation between tooth location and the severity of postoperative discomfort, 6-and 18-hours following treatment.

Ali et al [7] study states post-operative pain in mandibular teeth was much higher, the same reported in various other studies as well [26,27,30]. This may be because the mandible's cortically thicker plate than the upper jaw and dense trabeculae pattern results in reduced blood flow, increased localization of infection, and increased pressure compared to the maxilla, which may cause pain and slow healing [7, 50, 51].

Apical Fenestration:

The American Association of Endodontics defined apical root fenestration as a window-like defect in the alveolar cortical plate frequently exposing a part of the root, but the defect does not involve the margin of the alveolar bone. Apical fenestration may occur in 9% of cases and may be an anatomic predisposition to persistent pain after root canal treatment. Root canal treatment in a tooth with root fenestration may cause pain during palpation of the root apex and may cause persistent pain. In the absence of mucosal fenestration, the signs and symptoms of root fenestration can be mistaken for non-odontogenic disease. Periapical radiographs cannot diagnose root fenestration as effectively as CBCT. Repeated non-surgical root canal treatment may cause an apical root fracture and fail to relieve discomfort when there is root fenestration. Root resection relieves pain unless the fenestration is accompanied by a fracture [52, 53].

Effect of Pulp and Periapical Condition on endodontic operative pain

Six hours post endodontic treatment [6], root canal-treated (RCT) teeth with a previous history of irreversible pulpitis induced a significantly higher incidence (63.8%) and severity of post-endodontic pain [31] than RCT of teeth with a previous history of necrotic pulp (38.5%) or of retreated teeth (48.8%) [6,27,32]. 18 hours after treatment, no such correlation was identified [6]. The injury to the periapical vital tissue during endodontic treatment in teeth with irreversible pulpitis may encourage more intensive secretion of inflammatory mediators like prostaglandins, leukotrienes, serotonin, histamine, and bradykinin, all of which are also pain mediators [10]. This may explain why post-operative pain is more common and severe in teeth with irreversible pulpitis / vital pulp [6]. A higher incidence of postoperative pain in teeth without periradicular lesions [54, 55] might be attributed to a lack of space for pressure release when periradicular bone resorption is absent [5].

Sequeira *et al* [10] reported a relationship between pulpal necrotic teeth and painful apical pathosis and flare-up rates. Results have shown that the incidence of pain during endodontic treatment was 6.66% in vital teeth and 21% in non-vital teeth (necrosis). Post-obturation pain occurred in 18.75% of vital teeth and 13.15% of non-vital teeth (necrosis) [56]. This may be explained by the fact that extrusion of the virulent clonal types of pathogenic bacteria species (present in the root canal system initially responsible for the pre-operative symptoms) into the periradicular tissue during instrumentation will have the potential to cause or exacerbate periradicular inflammation than non-virulent microorganisms that did not cause a pre-operative symptom [10]. Periapical lesion size >5-10 mm, remained one of the most robust predictors of flare up, post-operative pain and failures [29, 57]. In teeth with unhealthy periodontium, bacteria can enter through the cementum into dentinal tubules.

However, certain studies found that there was no statistically significant distinction in postoperative pain between the vital and nonvital groups at all recorded time intervals [7, 58, 59]. Studies indicate that pain reactions seldom occur when a fistula is present [50].

Preoperatively symptomatic teeth

ElMubarak et al [34] reported that postoperative pain developed in 15.9% of the patients with a history of preoperative pain, whereas 7.1% had postoperative pain among those without a history of preoperative pain.

Numerous studies have also shown that there is a strong correlation between the presence of preoperative pain and the incidence of postoperative pain [4, 7-9, 25-30, 60,61]. This finding could be explained by the presence of preoperative infection of the root canal system and periapical area. This initially inflamed tissue may become secondarily inflamed during treatment [7]. Preoperatively symptomatic teeth may still experience hyperalgesia and allodynia caused by both peripheral and central mechanisms, even after dental treatment has been completed. Thus, patients with increased preoperative pain have a higher risk of experiencing postoperative pain [61-63].

The results showed that severe postoperative pain was usually reduced to a tolerable level within 3 days [64]. It also shows that the persistence of preoperative pain postoperatively may be a sign of an improving condition if the severity is reduced [2].

Tooth fracture or Root fracture

Preoperative split root, fractured cusp, or fractured tooth root should be accurately evaluated

because they are prevalent causes of pain that go untreated or become misdiagnosed. Patients aged 45 to 60 years are most likely to experience posterior teeth with vertical root fractures. Mild pain around the broken tooth is one of the symptoms that are most frequently observed, along with swelling, a fistula, and a deep pocket in just one location of the attachment surrounding the tooth. The x-ray sign that can be seen most frequently is a radiolucent periradicular band [65, 66]. Though one effective treatment option for cracked posterior teeth is root canal treatment, the presence of an associated periodontal pocket results in a lower survival rate [67].

INTRAOPERATIVE FACTORS: NON-MICROBIAL

Rubber dam

Proper isolation is a necessity for endodontic therapy to be successful. B. Heling and I. Heling stated [68] in 1977 that endodontic procedures should never be carried out without the use of a rubber dam.

Rubber Dam enhances the effectiveness of every endodontic treatment procedure by increasing visibility, enhancing visual access to the root canals, ensuring proper moisture control, and retraction of the soft tissue. Utilizing a rubber dam also lowers the risk of secondary microbiological contamination and patients ingesting or inhaling irrigants, hand files, or infected tooth debris. The Rubber Dam, then, represents the essential Gold Standard of Care in endodontic practice [69].

Single Visit vs Multiple Visit Root Canal Treatment

Factors that warrant multiple endodontic treatment visits (2 or more visits) are (i) the complex anatomy of the root canal system (ii) the organization of the microbial flora as biofilms [70] in inaccessible areas of the canal system that cannot be removed by instruments and irrigation in single visit treatment (iii) patient and/or dentist's fatigue: and (iv) clinical finding of the need for placing intracanal medicament [71] . The last factor is justified since several studies have shown that even after careful chemomechanical preparation, microorganisms can survive in the root canal system and in addition, they grow and multiply in the root canal system, where irrigating solutions and instruments are not able to reach, favoring the perpetuation of the periradicular lesion and treatment failure, thereby emphasizing the need for using intracanal medication between sessions to reduce microbial population [71]. Studies suggest that the use of intracanal medicaments containing calcium hydroxide decreased the microbial flora of the root canal system in a two-visit protocol compared to a single-visit protocol [70, 72].

But according to Roane *et al.* [73] and other researchers [55,74,75], more patients experience pain after endodontic treatment that is completed over several visits as opposed to just one visit.

However, in other published studies [7,34,76-80], there was no discernible difference between single and multiple visits for root canal treatment in terms of radiologic success or post-operative pain. Neither a single-visit root canal treatment nor multiple-visit root canal treatments can fully prevent short- and long-term complications. Patients undergoing a single visit might experience a slightly higher frequency of swelling and refer significantly to more analgesic use [6, 76].

In general, root canal treatment can be completed in a single visit when clinical conditions such as a vital tooth, lack of apical periodontitis, dry canals, and absence of apical bleeding at the time of root canal filling are seen biofilms [71]. Multiple sessions are suitable for cases wherein clinical conditions are unfavorable when the intracanal medicament dressing is indicated to reduce microbial flora in necrotic teeth, in complex root canal anatomy, and in the emergence of so-called acute exacerbation/relapse.

More important than the number of sessions in treatment is the existence of a shaped clean root canal system without exudation and no signs and symptoms reported by the patient and the dentist with sufficient time for the dentist to complete the final obturation [71,79].

Instrumentation:

The presence of infected and necrotic pulp tissue within the root canal system acts as a continuous irritant to the periapical tissue and thereby needs thorough root canal debridement.

Access preparation: An access opening that is misaligned and under-extended often causes root or furcal perforations and tooth loss unless surgically corrected [38]. And over extended access preparation weakens the tooth structure.

Working Length (W/L): The root apical constriction is not present (i) when roots are not fully formed (ii) it might also be resorbed due to inflammation of peri radicular tissues (iii) iatrogenically destroyed by an overzealous over-instrumentation due to incorrectly measured W/L.

If W/L measured is too long, the apical constriction at the physiological apex of the root is destroyed. Iatrogenic over-instrumentation promotes the enlargement of the apical foramen, infected debris and root canal filling material is extruded into the periodontal tissues, periodontal tissues are being mechanically stimulated which may permit an increased influx of exudates and blood into the root canal. This will enhance the nutrient supply of the remaining bacteria within the root canal, therefore, microorganisms left in the root canal can multiply and proliferate in the beneficial conditions [10, 81-83].

The success and prognosis of endodontic therapy are diminished if the W/L measured is too short because bacteria and pulp remnants are left in the apical part of the canal [81, 84].

The anatomy of the tooth, location of the apical foramen, curvature of the root canal, and dental radiological examination technique all affect the accuracy of the radiographic W/L of dental root canal measurements [85]. According to Weine [86], the W/L measured by the dental radiograph relies on the health of the root and periodontal tissues: If no alveolar bone and root resorption are found, the distance of W/L from the radiological apex of the root should be 1 mm; if alveolar bone resorption is found, the distance should be 1.5 mm; and if both are found, the distance should be 2 mm from the radiological apex. Whereas David [87] in his study reported the position of the apical foramen often to be 0.5mm short of the radiographic apex.

It is impossible to localize the conjunction area of cementum and dentine using the radiological W/L evaluation technique alone. Additionally, radiographic images may be distorted, and roots and adjacent structures may overlap [81]. Due to x-ray angulations, deviated foramen, or superimposed images, something that looks to be 0.5 to 2 mm from the radiographical apex may be ending in the periradicular tissue. The avoidance of instrumentation beyond the apical foramen is not guaranteed by a radiographic working length that is 0–2 mm short of the radiographic apex [88]. Thus, the results of both the electronic apex locator and radiological data must be combined [81, 88-91]

Apical patency, Glide path: It is recommended to maintain the apical patency, by using only either #6, #8, or #10K File and making it go 0.5mm beyond the measured working length [90,92], to avoid debris accumulation and thus obstruction formation of the apical region during treatment. By enabling the irrigation solution to reach the apical third of the root canal without being blocked by apical debris, the irrigation procedure will be improved. There is also evidence that maintaining apical patency and recapitulation does not increase postoperative pain in teeth with vital/nonvital pulp compared with non-apical patency. Furthermore, maintaining apical patency did not result in flare-ups or increased pain medication use [93, 94]. The risk of post-operative pain may be reduced by performing apical patency and glide path prior to root canal instrumentation. It helps maintain the natural canal curvature. Creating apical patency results in less debris extrusion [11, 95].

Crown Down technique: The method of "crown down" preparation that involves cervical pre-flaring [10,11, 96], proved to be most effective as regards to prevention of postoperative pain, due to better file control during apical area instrumentation by prior canal orifice preparation and so less apically extruded debris [97].

Rotary Files vs. Hand Files: Both incidence and intensity of pain are significantly lower after preparation with rotary instruments [11, 98] in comparison to reciprocating systems and hand files. The cross-section and taper of the instrument affect the debris space and its removal efficiency. Apical preparation of the root canal determines the risk of physiological foramen transportation or foramen enlargement (over-preparation), leading to an increased incidence of and longer-lasting postoperative pain [99, 100].

In the case of over-instrumentation of the root apical third, studies [11, 101] showed that in teeth with necrosis and apical periodontitis, postoperative pain in the group with an enlarged foramen (over instrumentation) was higher in the first days after treatment than in cases of no over-instrumentation.

Broken Instruments: Broken instruments were present in 9.33% of total retreatment cases and the incidence of instrument fracture increased with aging. 37.14% of cases with broken instruments have spontaneous pain [23]. Rotary instruments tend to fracture inside the canals when either the law of access cavity preparation is not followed, or when rotary instruments are not used according to manufacturer guidelines. As a result of instrument fracture, it becomes difficult to disinfect and obturate the canal apical to the tip of the fractured instrument (due to limited access to the apical part of the root canal) leading to persistent infection in the area.
The stage of instrumentation at which the instrument breaks can also affect the prognosis.

Oral Pulse granuloma / Periapical Pulse granuloma

Oral Pulse granulomas are clinically relevant because vegetable food particles, particularly pulses from leguminous plants can invade the periapical tissue through the root canals of teeth exposed to the oral cavity due to trauma/caries damage/or endodontic treatment (if tooth access cavity is kept open for drainage or when temporary filling placed in between endodontic appointments falls off exposing the root canals to oral cavity) [102-104]. Antigenic proteins, among other components of pulses, may play a role in the pathogenic tissue response (foreign body reaction) [105].

Root Canal Irrigation

J. D. Regan and Fleury [106] state that the complex and varied root canal system cannot be adequately debrided and cleaned with instrumentation alone. To facilitate chemomechanical debridement, the slogan should be "Shape, Clean, and Fill" rather than "Clean, Shape, and Fill". Irrigation protocol dissolves tissues, lavage, eradicates microbes, removes debris, lubricates during instrumentation of the root canal, and removes the smear layer. Disruption of biofilms is essential for preventing endodontic infections [107].

The most widely used irrigating solutions are saline, sodium hypochlorite, and chlorhexidine. The

solution most widely used as a chelating agent for the removal of the inorganic part of the smear layer is ethylenediaminetetraacetic acid [107,108]. Sodium hypochlorite, chlorhexidine, MTAD (mixture of doxycycline, citric acid, and a detergent) and Tetraclean (also a doxycycline-based endodontic irrigant composed of an antibiotic, an acid, and a detergent) act against the planktonic form of Enterococcus faecalis [109]. The protocol recommends mechanical debridement and copious irrigation for a minimum of twenty minutes with 2.5% to 5.25% solutions of sodium hypochlorite, followed by a rinse with a 17% solution of ethylenediaminetetraacetic acid and (sometimes) a final rinse with 2% chlorhexidine. The canals are dried with high-volume aspirators and sterile paper points [106].

Table 3: Different studies on Root canal Irrigation

Author	Study	Methods	Result
Tuna Kaplan *et al.,* 2022 [110]	A randomized clinical trial	Group1: conventional irrigation Group 2: a sonic irrigation activation system Groups 3: conventional irrigation + laser Group 4: sonic irrigation activation + laser	There was no statistically significant difference among the groups regarding efficacy, post-operative pain, and analgesic intake
Lucas Orbolato Chalub *et al.,* 2022 [111]	Postoperative pain with ultrasonic versus conventional irrigation (Research until May 2021)	All the studies used sodium hypochlorite (NaOCl) as the irrigant solution although this ranged from 2.5% to 5%.	Ultrasonic irrigation presented less occurrence of postoperative pain than conventional irrigation.
Ruksakiet K *et al.,* 2020 [112]	A Systematic Review and Meta-analysis of Randomized Controlled Trials, literature review until March 2020	Antimicrobial Efficacy of Chlorhexidine (CHX) and Sodium Hypochlorite (NaOCl) in Root Canal Disinfection	both CHX and NaOCl can reduce bacterial infections
Kusum Bashetty, Jayshree Hegde [113] 2010	A randomized clinical trial	Comparison of 2% chlorhexidine and 5.25% sodium hypochlorite irrigating solutions on postoperative pain	More pain was present in teeth irrigated using 5.25% sodium hypochlorite when compared to that in teeth irrigated using 2% chlorhexidine solution at 6hr only post-treatment
Ahmed Alkahtani, Tala D Al Khudhairi & Sukumaran Anil [114] 2014	A comparative study of the debridement efficacy and apical extrusion of dynamic and passive root canal irrigation systems	Group 1: irrigation using the EndoVac irrigation system. Group 2: irrigation was performed using a 30-gauge, tip-vented irrigation needle. Group 3: Using a 30-gauge, side-vented irrigation needle.	EndoVac irrigation system extruded less irrigant solution and least apical debris collection than either needle irrigation system.

Because of its effectiveness in dissolving pulpal tissue and antimicrobial activity, sodium hypochlorite (NaOCl) is the most widely used irrigating solution in endodontics. Sodium hypochlorite accident (extrusion into the periapex) can cause violent tissue reaction characterized by Hulsmann's criteria [115]- immediate acute severe pain, rapidly increasing swelling depending on the site of NaOCl injection, redness, profuse hemorrhage through the tooth, interstitial bleeding with ecchymosis, bruising of the skin and mucosa and numbness or weakness of affected nerve and in some cases development of secondary infection, sinusitis and cellulitis [23, 82, 116, 117].

Intracanal Medicament

Intracanal medication has been advocated in infected root canals and apical periodontitis in between endodontic appointments [10,118] and their role is secondary to shaping and cleaning of the root canal. Thorough canal debridement and adequate canal preparation are more important [119]. If the tooth does not respond to treatment, a bacteriological sample may be needed to help with the choice of intracanal medicine. After canal instrumentation, an intracanal medication is placed to (i) eradicate or inhibit the growth of any remaining microbial flora (ii) lessen inflammation of periapical tissue and pulp remnants (iii) neutralize tissue fragments and render the canal contents inert (iv) serve as a barrier for leaks from the temporary filling (v) help to dry persistently wet canals (vi) stimulate repair [119, 120]

Various intracanal medications include calcium hydroxide, triple antibiotic pastes [121], double antibiotic paste [122, 123], Ledermix paste (corticosteroid-antibiotic compound [124], and 2%-chlorhexidine gel [125].

Calcium hydroxide is universally suitable for use as an intracanal medicament, it is stable for extended periods of time, harmless to the body, and has a limited area of bactericidal action [126]. Additionally, it promotes the development of hard tissues and has potent anti-inflammatory effects. Calcium hydroxide alters

bacterial cell walls and denatures a potent endotoxin, lipopolysaccharide, thereby making bacteria less antigenic [127, 128]. Studies have reported that its effectiveness can be increased when used in combination with other medicaments like chlorhexidine and camphorated monochlorophenol (CMCP) [125]. Nano-calcium hydroxide has been proven to have advantages over normal calcium hydroxide [129], supporting its use as an intracanal medicament. Nano-calcium hydroxide mixed with propylene glycol showed alkaline pH and adequate release of calcium ions for 30 days.

Studies indicate that intracanal medication during endodontic treatment does not result in endodontic flare-ups but rather lessens pain between appointments [125]. In necrotic teeth with apical periodontitis, intracanal medication placement is preferable in between visits [122,128].

Cellulose Granuloma:

Apical periodontitis developing against particles of cellulose-containing endodontic materials [102, 130] has been denoted as cellulose granuloma. Plant materials' cellulose acts as a granuloma-inducing agent [105]. Sterile and medicated cotton wool and endodontic paper points particles have the potential to press or dislodge into the periapical tissue [130], resulting in a painful foreign body reaction at the periapex. The cellulose in cotton wool and endodontic paper tips is resistant to breakdown by human body cells. The foreign body reaction around them stays in periapical tissues for extended periods of time [102,131] allowing a biofilm to develop all around it. As a result, apical periodontitis persists and even worsens after root canal treatment, leading to treatment failure.

Intracanal Sealant:

Endodontic sealers fill the spaces between the obturating material and the walls of the root canal and between the gutta-percha cones, to form a coherent single mass of obturating material without voids. Discrepancies and irregularities between the gutta-percha filling and the canal walls, accessory canals, and numerous foramina are anticipated to be filled by the sealer. It is expected that by acting germicidal, it will also eliminate any bacteria that may have remained in the root canal after shaping and cleaning [132].

Table 4: Recent Studies on Intracanal Sealers:

Author	Study	Result
Melis Coşar *et al.,* 2023 [133]	mineral trioxide aggregate (MTA)-based bioceramic vs and resin-based sealers	Mineral trioxide aggregate showed a similar success rate and post-obturation pain incidence and intensity as AH Plus sealer and can be used as a root canal sealer in asymptomatic mandibular molars with irreversible pulpitis.
Anita Aminoshariae *et al.,* 2019 [134]	The impact of sealer extrusion on the endodontic outcome: A systematic review with meta-analysis	Sealer extrusion had a 32% higher risk of contributing to a non-healing outcome than no extrusion.
Marcelo Augusto Seron *et al.,* 2023 [135]	Postoperative pain after root canal filling with bioceramic sealers: a systematic review and meta-analysis of randomized clinical trials	The results showed that bioceramics sealers reduced postoperative endodontic pain only after 24 h and showed less sealer extrusion compared to the AH Plus sealer.
Emma Carr *et al.,* 2022 [136]	Do resin-based sealers increase postoperative pain following root canal treatment?	There is no significant difference in postoperative pain when resin-based root canal sealers are used when compared to other root canal sealers. For both resin and non-resin sealers, analgesics use, pain incidence post-operatively and intensity of pain reduce after 24 hours.
Cynthia Maria Chaves Monteiro *et al.,* 2023 [137]	Effect of endodontic sealer on postoperative pain: a network meta-analysis: epoxy resin-based, calcium silicate-based, zinc-oxide eugenol-based, and calcium hydroxide-based sealers.	No significant difference (with low certainty of the evidence) was detected in the risk and intensity of postoperative pain in the comparisons between eugenol-based, calcium hydroxide-based, epoxy resin-based, and calcium silicate-based endodontic sealers.

Anatomical structures nearby are harmed by the extrusion of root canal sealers. Clinical signs include pain, edema, paresthesia, and anesthesia. A case of endodontic sealer overfilling in the mandibular canal has been documented, resulting in tooth discomfort and numbness in the left lower lip and chin. After two months of corticosteroid therapy for the patient, a clinical evaluation revealed a better clinical state with the removal of the hypoesthesia but still had continued persistent discomfort and pain [138, 139].

Obturation

The first 24 hours saw the highest prevalence and severity of post-obturation discomfort, according to Harrison *et al.,* [140]. 99.1% of patients were symptom-free 60 days after obturation.

If standard safety precautions are followed, the types of root canal instrumentation and obturation techniques do not significantly alter the patients' post-operative pain [141]. Whether using the warm vertical compaction technique with gutta percha and epoxy resin-based sealer or the sealer-based filling technique with single cone gutta percha and calcium silicate-based sealer [142], the pain in symptomatic irreversible pulpitis teeth subsides in 48 hours after endodontic treatment.

However, Luis *et al.,* study [143] (cold lateral compaction of gutta-percha vs. Thermafil technique vs. Backfill - Thermafil obturation technique) found a significant association between postoperative pain and the obturation technique employed during root canal treatment. Patients who had their teeth filled with Thermafil obturators experienced much more discomfort than those who had their teeth filled using either of the other two methods.

Overextended and underextended obturations are linked to less favorable outcomes than adequate obturations, according to a study by Mello et al [144] on the influence of obturation extent on the result of root canal therapy. The results of an in vivo histological study by Ricucci et al [145] showed that in the presence of vital or necrotic pulps, the most favorable histological conditions were when the instrumentation and obturation remained at or just short of the apical constriction.

When the gutta-percha was extruded into the periapical tissue, there was always a severe inflammatory reaction (foreign body reaction) due to unnecessary mechanical and chemical irritation, which hinders the healing of the periapical tissue and thus reduces the probability of a successful outcome. Causes of overfilling [38] (i) Not correctly determining the exact location of the apical foramen, an absence of apical stop, or absence of apical constriction in mature teeth. (ii) Incorrect selection of master cone (iii) open apices. The patient may experience localized, sharp pain after the procedure with overfilling [82], even despite a previously clinical absence of pain. The accumulation of macrophages around the extruded gutta-percha impaired the healing of apical periodontitis [23,102,146]. Endodontic overfilling is only appropriate when it is accompanied by apicoectomy, during which the extruded foreign material is completely eliminated.

It was also noted that a maximum number of teeth with failed root canal treatment (47.7%) were obturated with root filling ending more than 3mm short of the radiographic apex [147]. Causes of short obturation filling may be due to inadequate canal preparation in blocked canals. Ledges and calcifications are most seen in failed endodontically treated teeth [77,148,149]. Improper obturation failure also occurs [38] when gutta-percha fills the canal to the apical foramen but does not obliterate the canal space laterally, if the master cone binds tightly in the middle third or coronal third of the canal but does not at the apical third and the tug-back resistance originates in the wrong area.

Sadaf et al [150] report in their study that obturation length was not found to be significantly associated with postoperative pain. It's well established that the persistence of infection is caused by the intracanal bacteria that still remain in the canal after shaping and cleaning.

MTA (mineral trioxide aggregate) obturation may play a role in the management of combined endo-perio lesions [151]. And because of MTA's excellent biological properties and ability to create a good seal without overextension of the filling material, it has been recommended for creating an artificial barrier in the apical area of teeth with large or open apices [152].

INTRAOPERATIVE FACTORS: MICROBIAL

Endodontic infections, resulting in pulpitis or apical periodontitis, are polymicrobial [102, 153]. Necrotic pulps offer an environment that is favorable for the development of various distinct oral bacterial species, especially strictly anaerobic bacteria. A correlation between the frequency of flare-ups and pulpal necrotic teeth with painful apical pathosis was proven by Siqueira et al [10].

The microbes, which are present in the complex root canal system within the small accessory canals/apical ramifications anastomoses, in the space between the root fillings and canal wall or within the innermost portions of infected dentinal tubules, grow in biofilms and as planktonic cells suspended in the canal's fluid phase [102,154]. These inaccessible areas serve as a reservoir for endodontic reinfection [155] even after root canal treatment and interfere with periapical healing [102,156-158]. Due to its anatomical placement, root canal infections cannot be treated with systemic antibiotics or the host's defence systems since the lack of a blood supply in the necrotic root canal prevents the delivery of systemic antibiotics and defence cells and molecules to the infected area. Only mechanical and chemical methods can be used to eradicate intracanal microbes [159-161]. When microbes enter the highly vascularized periradicular tissues, host cells often successfully eradicate them, stopping them, in most cases, from spreading to other places.

Siqueira *et al.,* [162] found that Bacteroides forsythus, Porphyromonas gingivalis, Streptococcus constellatus, Prevotella intermedia, Fusobacterium nucleatum and Fusobacterium periodontium are the most

prevalent species in endodontic cases diagnosed as acute apical abscess. All teeth in patients who were reported to be in severe acute pain displayed F. nucleatum [163]. The periapical tissue of cases with clinical symptoms of acute exacerbation, acute abscesses, and draining sinuses also consistently contains F. nucleatum [154].

Enterococcus faecalis is found in persistent endodontic infections that cause biting discomfort (24% to 77%) [102,164-166]. E. faecalis is an opportunistic organism from elsewhere in the mouth, which grows in exposed root canals [167] and may survive without nutrition [102,168]. It competes with other microbes and invades dentinal tubules. E. faecalis can tolerate a pH of up to 11.5 and is resistant to the majority of intracanal medications [102]. In all stages of the endodontic retreatment, P. gingivalis and E. faecalis predominate [169].

Imbalance of root canal microbial flora: In multi-visit endodontic treatment, the chemo-mechanical preparation of the root canals should be completed in a single appointment, and intracanal medications placed in between visits [10]. The synergistic balance between the bacteria in the root canals can be upset by incomplete chemo-mechanical preparation because it can remove some microbial species while leaving others behind, which can subsequently overgrow [163]. The inflammatory response is therefore exacerbated by the virulent genes of left-over pathogenic strains, the injury to the peri radicular tissues may be intensified, and this may lead to a worsening of the lesion [10]. Instrumentation short from the apical constriction, missed canals, and anatomical complexities of the root canal space, such as c-shaped canals, deltas, multiple foramina, and furcation accessory canals are also examples of some situations in which incomplete chemo-mechanical debridement may cause postoperative pain [170].

Increase of the oxidation-reduction potential: Primary pulpal-periapical infections have an abundance of anaerobic bacteria. However, oxygen infiltration of the root canal during treatment may promote the overgrowth of facultative bacteria that resisted chemo-mechanical intervention [10]. All the microbes isolated from teeth presenting with acute pain during endodontic therapy were aerobic and facultative microbes, mainly facultative streptococci and gram-negative microbes, no obligate anaerobes were isolated [102,171]. Changes in tissue redox potential have been suggested as the etiology of exacerbations of cellulitis during root canal therapy [10, 171].

Bacterial extrusion into periapical: Apical periodontitis is an inflammatory condition of the periradicular tissues brought on by a lingering microbial infection in the infected tooth's root canal system [172, 173]. There is a delicate balance between the host defense in the peri-radicular tissues and the microorganisms in the infected root canal in asymptomatic chronic periradicular lesions associated with infected teeth [10]. In scientific literature, this phenomenon is referred to as "local adaptation syndrome" [174]. The microbial density in 5mm of the infected apical root area is exceedingly high, with predominating anaerobic microorganisms. The apical root canal area is described as "dangerous" [175] because of its complex structure (accessory canals, apical deltas) and high bacteria density. Microbial extrusion to periapex causes the periradicular tissue to respond with an acute inflammatory response as the body mobilizes an acute inflammation to restore equilibrium [10]. The most typical reason for flare-ups is microbial damage to the periradicular tissues [120].

Machado et al [173] in their study reported higher contents of cultivable bacterial microbial load and lipopolysaccharides in primary apical periodontitis. However, post-treatment apical periodontitis presented a more varied microbiota. A higher lipopolysaccharides concentration results in more periapical bone destruction [102].

According to Sjogren et al [176], some periapical lesions are perceived as healing even though the infection was still present in the canals at the time of root filling, because bacteria may be present in numbers and virulence that may be sub-critical to sustain the inflammation of the periapex [71]. However, later, such residual microbes can also delay or prevent complete periapical healing.

There have also been reports of intraradicular fungi (the most prevalent of which is Candida albicans) [177] and yeasts [102,178] in root-treated teeth with unresolved apical periodontitis.

Secondary radicular infection:

Microorganisms that are not present in the primary infection but enter the root canal system during treatment, in between appointments, or after endodontic treatment are what cause secondary radicular infection [10]. The main causes of microbial recontamination of root canals are: not adhering to the aseptic guidelines during the endodontic procedure, inadequate patient oral hygiene, dental plaque, calculus, or caries on the tooth crown, leaking rubber dams, contamination of endodontic instruments or via leaking non-hermetic coronal restorations [179], fractured teeth, or when the tooth is purposefully left open for drainage [10, 180], and through the apical foramen either through the periodontal ligament, periodontal pocket, or through fistulas or hematogenically [175].

Extraradicular infections do occur in exacerbating apical periodontitis lesions [154] and in infected periapical pocket cysts with cavities open to the root canal and periapical actinomycosis [102]

Periapical actinomycosis: Periapical actinomycosis is a cervicofacial form of actinomycosis [102,181]. It is possible to isolate Actinomyces israelii, a commensal of the oral cavity, from tonsils, dental plaque, periodontal pockets, and carious lesions [182]. Even after receiving adequate root canal therapy, they might still cause periapical irritation. For teeth that did not respond to proper non-surgical endodontic treatment, Actinomyces israelii and P. proprionicum were routinely isolated from their periapical tissue [182].

Extraradicular Virus: Studies have revealed an association between Human Cytomegalovirus and Epstein-Barr virus and the acute exacerbation of periapical lesions [102, 183, 184].

According to a study by Lars *et al.,* [185], healing took place regardless of the quality of the root filling when no bacteria were present during root canal therapy. Conversely, when root canal microbes persisted, poor-quality root fillings exhibited a higher connection with non-healing than fillings that were technically sound. This study demonstrates how crucial it is to have a bacterial-free root canal system prior to obturation to create the best possible healing environments for periapical tissues. The presence of stainable bacteria in the canal was associated with the severity of periradicular inflammation. Stainable bacteria inside the canal [186] were frequently accompanied by swelling, discomfort, or a draining sinus tract.

To prevent/minimize endodontic operative pain to a great extent, iatrogenic errors must be avoided:

• Need proper case selection: The purpose of case selection is to determine the feasibility and practicability of root canal treatment and to avoid treating cases that will fail regardless of the best treatment. Many root canal treatment failure cases are attributed to poor case selection. Misaligned teeth are not restorable and can cause secondary periodontal problems.

• A good preoperative radiograph is mandatory.

• Need complete aseptic condition (Use of Rubber Dam) to be maintained during all intracanal procedures.
• A proper root canal working length.

• Prevention of root or furcation perforation: Root perforation was present in 5.6% of treated cases, and 57.14% of them had spontaneous pain [23]. Root or furcation perforations can occur pathologically as a result of resorption and caries or iatrogenically during the preparation of access cavities (high potential areas for furcation perforation are the floor of molars and two rooted maxillary premolars roots that are narrow mesiodistally and broad buccolingual with curved canals), mid-root and apical third perforation, post space preparation, or may occur as a result of the extension of internal resorption into periradicular tissues. In his study [187], Frank reported that the presence of radicular perforations has been both difficult to determine and manage. It has also been reported in other literature that the repair of furcation perforations is unpredictable due to periodontal communication.

• Complete cleaning of root canals**:** The first visit to a multiple-visit root canal treatment is a significant step that, if professionally managed, can reduce the incidence of flare-ups [188]. Complete cleaning of root canals on the first visit does not allow any remaining bacteria that would proliferate if left behind. [10,120].

• Avoid missed canals/ untreated spaces: The overall prevalence of missed canals and untreated spaces among endodontically treated teeth with spontaneous pain was 18%-31.57%. The prevalence of missed canals was as high as 40.6% in maxillary first molars. 90% of the teeth with missing canals had apical periodontitis overall (MB2 upper molars; middle mesial or distal canals in lower molars; extra canals in anterior premolars, invagination, palatal groove in central incisors). Inadequate access openings make it difficult to locate the supplemental canals. Bacteria residing in these canals lead to the persistence of symptoms [23,77,189, 190].

• The use of Intracanal Medicaments between endodontic appointments especially in the treatment of infected cases [10], will reduce any remaining microbial flora in the canal and not allow microbes to proliferate.

• Avoid extrusion of intracanal microbial flora/irrigation solutions/ intracanal medicament/ sealer/ obturating material into the periapex: The filling material must reach the root apex without overextending into periapical tissues or other adjacent structures. The unknown factors that could not be detected by radiograph include the complications of over-instrumentation and extrusion of intracanal irrigant into periapical during root canal treatment [23]. These factors comprised 16.26% of total examined cases and presented with 55.73% spontaneous postoperative pain [82, 120]. There are four different non-microbial iatrogenic causes that could harm tissue and result in the aforementioned symptoms: (i)chemical factors because the materials used to clean or fill root canals have neurotoxic effects (ii) core filling material or sealer can extrude from canal into the adjacent anatomical structures which can induce pressure phenomenon (iii) mechanical damage from over-instrumentation (iv) incorrect warm condensation techniques can also cause burning of tissues [191-193]. Intracanal bacteria, irrigation solutions, intracanal medications and sealants can invariably contact the periapical tissues causing periapical irritation through the wide apical foramen (resorption/ over instrumentation). Alternatively, if extreme pressure is applied during irrigation/placing intracanal materials, or if the tip of the needle becomes lodged in the root canal without the solution/material coronally draining from the root canal,

accidental forced injection beyond the apical foramen and into the anatomical structures [194] is possible. Although extrusion of very minute amounts of intracanal material is generally well tolerated by the periapical tissue, extensive extrusion of material and infiltration of the periapical tissue by microorganisms and their products can lead to clinical manifestations such as [195] pain with signs of local inflammation, tooth pain when tapping or touching the buccal alveolar process, swelling of the lips, dysesthesia, and paresthesia may occur especially when the extruded filling materials are either close to or in contact with nerve structures (Foreign body type reaction in connective tissue) [191-193]. The pain due to extrusion into the periapex can be spontaneous, intermittent, or permanent. The patient may also complain of a burning sensation, a feeling of 'pins and needles,' or pressure on the teeth [196]. Although every effort is made to keep the sealer inside the root canal space, accidental extrusion can happen during the obturation procedure. If the sealer remains a small 'puff" around the apex due to minor extrusion, a slight transient pain may occur. But if sealers extrude to adjacent anatomical structures, intense and persistent pain occurs. In the maxilla, root canal sealer can be extruded into the sinus and cause maxillary sinusitis, aspergillosis infection, paresthesia, and other related neural problems. Many authors contend that the extruded root canal filling material into the sinus behaves like a foreign body and does not stay in a fixed location of the maxillary antrum. The ciliated mucosal cells of the maxillary antrum tend to move towards the natural orifice, which may then become occluded. Stoppage of secretion leads to an anaerobic condition that favors the growth of Aspergillus spores in the sinus [197, 198]. Regarding the mandible, the main presenting symptoms of extrusion are pain, swelling and paresthesia. Paresthesia might be caused by the pressure of endodontic materials in the mandibular canal after its perforation by neurotoxic effects, reversible and irreversible blockage of nerve conduction, or alteration of the nerve membrane potential [138,139, 199].

• Need to avoid other Procedural errors: Endodontic treatment can be influenced by various other procedural errors such as overpreparation of canals, underfilling, separated broken instruments, apical transportation, and ledges, all of which can impact post endodontic pain. These procedural errors often arise from several factors, including a lack of understanding regarding root canal anatomy, mechanical instrumentation principles, and tissue wound healing. Consequently, these errors hinder the success of endodontic treatment and elevate the risk of treatment failure, particularly in cases involving teeth with necrotic pulp and periradicular lesions [200, 201].

• A tooth's root canal is not to be kept open for the purpose of drainage as more microbial cells, species and their products will gain access to the root canal and periradicular tissues. Also, teeth with subgingival breakdown, lacking coronal walls/full coverage, and degradation below the margins of their finished restorations would all permit the root canal system to become reinfected [10, 202]. 96.3% of dentists prefer delaying final permanent restoration to the next visit for symptom disappearance as per a study [179]. Closed coronal seal with temporary fillings are required between visits.

Hoen et al., [203] in their study reported that most of the retreated endodontic cases involved multiple causes. Eighty-five percent of the cases were presented with periradicular radiolucency. Obturation radiographic quality was poor in 65% of cases. Painful symptoms were found in 51% of cases. 42% of teeth had an untreated root canal space [200]. In 89% of the instances with prior radiographic asymmetrical obturations, additional canal space was discovered and treated. Evidence of coronal leakage was noted in 13% of the retreated teeth [203]. The presence of pathogens in the incompletely treated or untreated root canal system is the primary cause of periradicular infection [200].

POSTOPERATIVE FACTORS

Occlusal Reduction

The occlusal reduction should prevent postoperative pain in those patients whose teeth initially exhibit pulp vitality [204], percussion sensitivity, preoperative pain, and /or the absence of a periradicular radiolucency [205]. It was concluded that occlusal reduction did not have much effect for the first 24 hours to reduce post-operative pain, but the effect was observed in a 6-day follow-up [206-209].

Increased levels of inflammatory mediators that stimulate peri radicular nociceptors are the cause of the patient's complaints of sensitivity to biting and chewing. The occlusal reduction will lessen the sensitized nociceptors continued mechanical stimulation. [206].

Pharmacological role:

- **Analgesics:**

Elizabeth *et al.,* [37] reported that 39% of patients took oral analgesics for postoperative pain on day one. On postoperative day two, only 18% reported taking pain medication and by postoperative day five, only 4% reported taking pain medication. This study also identified genetic variants in COX-2 associated with post-treatment pain following endodontic treatment. NSAIDs that target COX-1 and COX-2 are the frontline treatment for post-treatment pain in endodontics [37]. NSAIDs like ibuprofen and naproxen usually affect both COX-1 and COX -2 enzymes, so they are called nonselective NSAIDs.

The studies suggest that the combination of paracetamol and ibuprofen was more effective (85% pain reduction) compared to using paracetamol or ibuprofen alone (64% pain reduction). Additionally, administering ketoprofen (50 mg) and naproxen (500 mg) 6 hours post-operatively also resulted in reduced post-endodontic

pain. This recommendation aims to minimize drug intake, which is particularly relevant for fragile and elderly subjects. [210-214].

Kumar G et al [215] study shows that the preoperative administration of anti-inflammatory drugs is an effective modality for reducing postoperative pain for up to 24 hours in teeth with irreversible pulpitis. Preoperative pain management may also lessen the likelihood of side effects that could result from the frequent use of postoperative painkillers.

- **Steroids:**

In endodontic patients, corticosteroids have a postoperative pain-reducing effect, and the choice of medication regimens may be a key predictor of pain relief. However, some studies report that post-operative opioids or corticosteroids did not significantly reduce postoperative pain [214, 216].

- **Antibiotics:**

Studies have shown that the use of an antibiotic after a root canal procedure on a symptomatic non-vital tooth has no impact on the degree of pain at 24 hours postoperatively. Prophylactic antibiotics also have no effect on the frequency of flare-ups after treating asymptomatic non-vital teeth. [7, 73, 217].

The American Dental Association and the American Association of Endodontists have both proposed antibiotic stewardship standards, which contrast with the idea of antibiotic pre-medications to control post-operative endodontic pain. Evidence suggests that antibiotics cause significant harm and only modest benefits for most post-endodontic pain. A correct diagnosis and an efficient endodontic procedure will reduce the microbial flora sufficiently for healing to take place [218, 219]. The expert panel recommends against using antibiotics for target conditions unless there is systemic involvement [218-221].

Indications for systemic antibiotics in Endodontics: The following situations call for adjunctive systemic antibiotic therapy in addition to endodontic therapy [37, 222] (i) Patients with medically compromised patients have an acute apical abscess (ii) Patients who have an acute apical abscess with systemic involvement (localized fluctuant swellings, elevated body temperature >38°C, tachycardia, general malaise, lymphadenopathy, mandibular trismus) (iii) Progressive infections (rapid onset of severe infection in 24 h, cellulitis, or spreading infection, osteomyelitis) where oral surgeons may need to be consulted immediately (iv) Replantation of avulsed permanent teeth [223], in these circumstances, topical antibiotics may also be recommended. [224] (v) Deep soft tissue injuries that need to be treated (such as with sutures or debridement) [225].

Contra-indications for systemic antibiotics in Endodontics: Most endodontic infections are confined within the tooth and can be successfully managed by established local operative treatment [226], drainage, and rarely, local or systemic antibiotics. The following cases do not call for the use of adjunctive systemic antibiotic therapy during endodontic treatment [222, 227] (i)Symptomatic irreversible pulpitis (pain without any additional symptoms or infection-related signs) (ii) Pulp necrosis and (iii) Symptomatic apical periodontitis (pain on percussion, biting, and widening of the periodontal ligament space) (iv) Chronic apical abscess (teeth with periapical radiolucency and sinus tract) (v) Acute apical abscess (localized fluctuant swellings) without systemic involvement.

To exceed the minimal inhibitory concentration, avoid side effects and stop the development of resistant bacteria, antibiotics must be prescribed at the proper frequency, dose, and duration [228]. It is currently recommended to prescribe antibiotics for three days and then review the patient as part of general antibiotic stewardship; additional antibiotics should only be prescribed if clinically indicated [229, 230].

Antibiotic prophylaxis in Endodontics: Medical conditions such as impaired immune function (Leukemia, HIV/AIDS, end-stage renal disease, dialysis, uncontrolled diabetes, chemotherapy, steroids, immunosuppressive post-transplant medications, inherited genetic defects) or risk of developing infectious endocarditis (patients with complex congenital heart defects, prosthetic cardiac valves, or a history of infective endocarditis), prosthetic joint replacement, patients whose jawbones are exposed to high-dose irradiation and patients receiving intravenous bisphosphonate treatment – these medical cases should only be taken into account[222] when considering the use of prophylactic antibiotics in medically compromised patients undergoing endodontics.

Other modalities to reduce post-endodontic pain:

Other adjunctive treatments, such as lower laser therapy [211, 231, 232], cryotherapy [233-236], and phototherapy [237] have been suggested to reduce post-operative endodontic pain.

Possible need for apical surgery in persistent apical periodontitis:

Post-treatment lesions following root canal treatment are most often associated with inadequate quality procedures that do not remove intra-canal infection [158], this scenario can be corrected by a nonsurgical re-treatment approach. However, some cases do require surgical intervention such as:

- Microbial infection remains (even after repeated orthograde shaping and cleaning root canal procedure) in the form of biofilms in inaccessible apical ramification areas, apical inter-canal isthmuses, apical accessory canals, extra radicular infection including apically extruded dentine debris with bacteria present in dentinal tubules and overly extruded endodontic intracanal materials. There is no evidence that the root filling can properly entomb these remaining germs in the apical canal system and render them harmless. Because of this residual root infection and or periapical foreign body reactions, post-treatment apical periodontitis which may be radiographically undetectable at the initial stages, may persist or develop as a defence mechanism to prevent the systemic spread of bacteria and/or their byproducts to other sites of the body. This, over time, creates persistent apical periodontitis that can be healed by periapical endodontic surgery removing the irritants.

- True Cystic Lesions / Cystic Apical Periodontitis: Cysts may occur in 6% to 55% of periapical lesions. The frequency of periapical granulomas is 9.3% to 87.1%, and that of abscesses is 28.7% to 70.07%. [23]. Radiographs alone cannot differentiate apical periodontitis into cystic and non-cystic diseases. There is consensus that all inflammatory periapical lesions should initially be treated conservatively rather than surgically [83]. A periapical pocket cyst (an extension of the apical part of the tooth into an incomplete epithelial lined cyst lumen) may heal during orthograde root canal treatment because it clears the root canal of much of the infectious material and stops reinfection by obturation [238]. However, there is always the chance that epithelial cells may be more activated, leading to further epithelial proliferation and formation of a complete epithelium-lined bag-like periapical true cyst [102,239,240], that is adjacent to but separated from the root apex. A true periapical (radicular)cyst grows larger or stays the same size over time even after completion of endodontic treatment. True cysts are not resolved by non-surgical root canal treatment because it is self-sustaining [239] and unaffected by the presence or absence of irritants in the root canal [238].

- Endogenous cholesterol crystals: Between 18% and 44% of chronic apical periodontitis lesions had an accumulation of endogenous cholesterol crystals [102,241,242]. The cholesterol crystals are thought to be released by the following sources: (i) dying lymphocytes, plasma cells, and macrophages in chronic periapical lesions; (ii) circulating plasma lipids [241] and (iii) disintegrating erythrocytes of the periapical lesion's stagnant blood vessels [242]. In persistent periapical lesions, locally dying inflammatory cells' disintegrating membranes may be the main source of endogenous cholesterol. In addition to being unable to break down the crystalline cholesterol, macrophages and giant cells that surround cholesterol crystals are also important sources of apical inflammatory and bone resorptive mediators.

Scar tissue healing / Periapical scar:

Occasionally, the defect caused by periapical inflammatory lesions may fill with dense fibrous collagenous tissue rather than normal alveolar bone [102, 240, 243] as a reparative response after a proper endodontic treatment /retreatment with or without periapical surgery. These fibrous periapical scars usually arise when both buccal and lingual cortical bone plates are missing [240], but sometimes can occur even in intact cortical plates area. Periapical scars may be misdiagnosed as a radiographic sign of failed endodontic treatment and is not a reason for endodontic surgery.

CONCLUSION

Endodontic operative pain can be minimized with proper care and attention. Informing patients about the possibility of experiencing pain during and after root canal treatment is essential. Dentists should always be cautious of unintended iatrogenic harm and be aware of the multifactorial etiopathogenesis of endodontic operative pain (Table 2). It is crucial to consider endodontic operative pain and persistent apical periodontitis following non-surgical root canal treatment as significant patient-centered outcomes.

REFERENCES

1. Bhardwaj, A., Gupta, R. K., Ates, A. A., Wahjuningrum, D. A., Arıcan, B., AlOmari, T., ... & Pawar, A. M. (2023). Comparison of Postoperative Pain after the Utilization of Different File Systems in Single Visit Endodontics. Patient preference and adherence, 17, 1025-1034. https://doi.org/10.2147/PPA.S405723
2. 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; 41:91–99. doi:10.1111/j.1365-2591.2007. 01316.x
3. Liran Levin, Alon Amit, Malka Ashkenazi. Post-operative pain and use of analgesic agents following various dental procedures. Am J Dent 2006 Aug;19(4):245-7.
4. Y-L Ng, J P Glennon, D J Setchell, K Gulabivala. Prevalence of and factors affecting post-obturation pain in patients undergoing root canal treatment. Int Endod J. 2004 Jun;37(6):381-91. doi: 10.1111/j.1365-2591.2004.00820. x.
5. Post-Operative Endodontic Pain Management. E Scholarly Community Encyclopedia. 10.3390/healthcare10050760
6. M. Gotler, B. Bar-Gil, and M. Ashkenazi. Clinical Study Postoperative Pain after Root Canal Treatment: A Prospective Cohort Study. International Journal of Dentistry Volume 2012, Article ID 310467, doi:10.1155/2012/310467
7. Ali, S. G., Mulay, S., Palekar, A., Sejpal, D., Joshi, A., & Gufran, H. (2012). Prevalence of and factors affecting post-obturation pain following single visit root canal treatment in Indian population: A

prospective, randomized clinical trial. Contemporary clinical dentistry, 3(4), 459-63. DOI: 10.4103/0976-237X.107440

8. N Polycarpou, Y-L Ng, D Canavan, D R Moles, K Gulabivala. Prevalence of persistent pain after endodontic treatment and factors affecting its occurrence in cases with complete radiographic healing. Int Endod J. 2005 Mar;38(3):169-78. doi: 10.1111/j.1362591.2004.00923.
9. N. Imura, M.L. Zuolo. Factors associated with endodontic flare-ups: a prospective study. Int.Endod J. September 1995 https://doi.org/10.1111/j.1365-2591.1995.tb00311
10. J F Siqueira Jr. Microbial causes of endodontic flare-ups. Int Endod J 2003 36: 453-463.
11. Zawrzykraj, E., Krużyński, W., Radwański, M., & Łukomska-Szymańska, M. (2022). Causes of post-operative pain related to root Canal treatment. Journal of Stomatology, 75(1), 201-205.
12. Sharma A, Mandlik J, Varghese R. An overview of etiology of endodontic flare-ups. Ind J Conserv Endod, 2016;1(3):76-80.
13. Weine FS. Endodontic Therapy Fifth edition, Mosby: 203-37.
14. Nixdorf, D. R., Moana-Filho, E. J., Law, A. S., McGuire, L. A., Hodges, J. S., & John, M. T. (2010). Frequency of nonodontogenic pain after endodontic therapy: a systematic review and meta-analysis. Journal of Endodontics, 36(9), 1494-1498. doi: 10.1016/j.joen.2010.06.020
15. Mattscheck D, Law AS, Nixdorf DR. Diagnosis of non-odonogentic toothache. In: Hargreaves KM, Cohen S, editors. Cohen's pathways of the pulp. 10. St. Louis, MO: Mosby Inc; 2011. pp. 49–70
16. Oshima K, Ishii T, Ogura Y, Aoyama Y, Katsuumi I. Clinical investigation of patients who develop neuropathic tooth pain after endodontic procedures. J Endod. 2009; 35:958–61
17. Allerbring M, Haegerstam G. Chronic idiopathic orofacial pain. A long-term follow-up study. Acta Odontol Scand. 2004; 62:66–9
18. M H Ree. An unusual swelling following endodontic and prosthodontic treatment of a mandibular molar due to a foreign body reaction. Int Endod J. 2001 Oct;34(7):562-7. doi: 10.1046/j.1365-2591.2001.00435
19. Hayes, M. H. S., and Patterson, D. G. Experimental development of the graphic rating method. Psychol. Bull. (1921). 18, 98–99.
20. Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H., ... & European Palliative Care Research Collaborative (EPCRC. (2011). Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. Journal of pain and symptom management, 41(6), 1073-1093.
21. Wolfe, Frederick, and Kaleb Michaud. "The Hawthorne Effect, Sponsored Trials, and the Overestimation of Treatment Effectiveness." The Journal of Rheumatology 37.11 (2010): 2216-2220.
22. Fox, J., Atkinson, J. S., Dinin, A. P., Greenfield, E., Hechtman, E., Reeman, C. A., ... & Todaro, C. J. (1970). Incidence of pain following one-visit endodontic treatment. Oral Surgery, Oral Medicine, Oral Pathology, 30(1), 123-130.
23. Sameer Hatem Abdul Haleem. Radiographic Assessment of Post-Endodontic Pain. Indian Journal of Forensic Medicine & Toxicology, April-June 2021, Vol. 15, No. 2.
24. Gao, X., Xin, X., Li, Z., & Zhang, W. (2021). Predicting postoperative pain following root canal treatment by using artificial neural network evaluation. Scientific reports, 11(1), 17243. https://doi.org/10.1038/s41598-021-96777-8
25. Aksoy, U., Pehlivan, S. & Buhara, O. The top risk factors for endodontic flare-up: a Monte Carlo simulation. Clin Oral Invest, 25, 3681–3690 (2021). https://doi.org/10.1007/s00784-020-03692-9
26. Arias, A., De la Macorra, J. C., Hidalgo, J. J., & Azabal, M. (2013). Predictive models of pain following root canal treatment: a prospective clinical study. International endodontic journal, 46(8), 784-793. doi: 10.1111/iej.12059. Epub 2013 Feb 12
27. Segura-Egea, J. J., Cisneros-Cabello, R., Llamas-Carreras, J. M., & Velasco-Ortega, E. (2009). Pain associated with root canal treatment. International endodontic journal, 42(7), 614-620. https://doi.org/10.1111/j.1365-2591.2009.01562
28. R Shresha, D Shrestha, R Kayastha. Post-Operative Pain and Associated Factors in Patients Undergoing Single Visit Root Canal Treatment on Teeth with Vital Pulp. Kathmandu Univ Med J (KUMJ) 2018 Apr-Jun;16(62):220-223.
29. Genet, J. M., Hart, A. A. M., Wesselink, P. R., & Thoden van Velzen, S. K. (1987). Preoperative and operative factors associated with pain after the first endodontic visit. International Endodontic Journal, 20(2), 53-64.
30. Alí, A., Olivieri, J. G., Duran-Sindreu, F., Abella, F., Roig, M., & García-Font, M. (2016). Influence of preoperative pain intensity on postoperative pain after root canal treatment: A prospective clinical study. Journal of Dentistry, 45, 39-42.
31. Nair M, Rahul J, Devadathan A, Mathew J. Incidence of Endodontic Flare-ups, and Its Related Factors: A Retrospective Study. J Int Soc Prev Community Dent. 2017 Jul-Aug;7(4):175-179. doi: 10.4103/jispcd.JISPCD_61_17. Epub 2017 Jul 31. PMID: 28852632; PMCID: PMC5558250
32. Lloberas J, Celada A. Effect of aging on macrophage function. Exp Gerontol. 2002; 37:1325–31.
33. Ozdemir, H. O., Buzoglu, H. D., Calt, S., Stabholz, A., & Steinberg, D. (2010). Effect of ethylenediaminetetraacetic acid and sodium hypochlorite irrigation on Enterococcus faecalis biofilm colonization in young and old human root

canal dentin: in vitro study. Journal of Endodontics, 36(5), 842-846.
34. ElMubarak, A. H. H., Abu-bakr, N. H., & Ibrahim, Y. E. (2010). Postoperative pain in multiple-visit and single-visit root canal treatment. Journal of Endodontics, 36(1), 36-39.
35. Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. Pain Forum. 1995; 4:209–21.
36. Montero, J., Lorenzo, B., Barrios, R., Albaladejo, A., Canelo, J. A. M., & López-Valverde, A. (2015). Patient-centered outcomes of root canal treatment: a cohort follow-up study. Journal of endodontics, 41(9), 1456-1461.
37. Applebaum, E., Nackley, A. G., Bair, E., Maixner, W., & Khan, A. A. (2015). Genetic variants in cyclooxygenase-2 contribute to post-treatment pain among endodontic patients. Journal of Endodontics, 41(8), 1214-1218.
38. Dr. Sadashiv Daokar, Dr. Anita.Kalekar. Endodontic Failures-A Review. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) Volume 4, Issue 5 (Jan.- Feb. 2013), PP 05-10
39. Glennon JP, Ng YL, Setchell DJ, Gulabivala K. Prevalence of and factors affecting postoperation pain in patients undergoing two-visit root canal treatment. Int Endod J 2004; 37:29-37.
40. Kaur, Maj Summerdeep, Awasthi Comparative evaluation of interappointment flare-ups in diabetic and in non-diabetic patients. Int. J. Curr. Res. 2020 12(01), 9301–9304.
41. Armada-Dias, L., Breda, J., Provenzano, J. C., Breitenbach, M., Rôças, I. D. N., Gahyva, S. M. M., & Siqueira Junior, J. F. (2006). Development of periradicular lesions in normal and diabetic rats. Journal of Applied Oral Science, 14, 371-375.
42. Maixner W, Fillingim R, Kincaid S, Sigurdsson A, Harris MB. Relationship between pain sensitivity and resting arterial blood pressure in patients with painful temporomandibular disorders. Psychosom Med. 1997; 59:503–511
43. Fillingim RB, Maixner W. The influence of resting blood pressure and gender on pain responses. Psychosom Med. 1996; 58:326–332.
44. Mini A, Rau H, Montoya P, Palomba D, Birbaumer N. Baroreceptor cortical effects, emotions, and pain. Int J Psych. 1995; 19:67–77
45. Rosenberg P.A. Clinical strategies for managing endodontic pain. Endod. Topics. 2002; 3:78–92. doi: 10.1034/j.1601-1546.2002.30108
46. Lavanya Bamini. Influence of Tooth Factors and Procedural Errors on the Incidence and Severity of Post-Endodontic Pain: A Prospective Clinical Study. Dent J (Basel). 2020 Sep; 8(3): 73
47. R J Gatchel. Managing anxiety and pain during dental treatment Review. J Am Dent Assoc. 1992 Jun;123(6):37-41.doi: 10.14219/jada.archive.1992.0194.
48. A. J. Van Wijk, J. Hoogstraten. Reducing fear of pain associated with endodontic therapy. International Endodontic Journal. 02 March 2006 https://doi.org/10.1111/j.1365-2591.2006.01090.
49. Lawrence Leung. Pain Catastrophizing: An Updated Review. Indian J Psychol Med. 2012 Jul-Sep; 34(3): 204–217 doi: 10.4103/0253-7176.106012
50. William H. Clem. Posttreatment Endodontic Pain. The Journal of the American Dental Association. Volume 81, Issue 5, November 1970, Pages 1166-1170
51. Alacam T, Tinaz AC. Interappointment emergencies in teeth with necrotic pulps. J Endod. 2002; 28: 375-7.
52. Alroomy R. Apical fenestration in endodontically treated teeth: A report of two cases. Niger J Clin Pract 2021; 24:1092-5.
53. Pasqualini, D., Scotti, N., Ambrogio, P., Alovisi, M., & Berutti, E. (2012). Atypical facial pain related to apical fenestration and overfilling. International endodontic journal, 45(7), 670-677. doi: 10.1111/j.1365-2591.2012. 02021.Epub 2012 Feb 6.
54. Ince B, Ercan E, Dalli M, Dulgergil CT, Zorba YO, Colak H. Incidence of postoperative pain after single- and multi-visit endodontic treatment in teeth with vital and non-vital pulp. Eur J Dent. 2009 Oct;3(4):273-9. PMID: 19826598; PMCID: PMC2761157.
55. Bhagwat, Sumita; Mehta, Deepil. Incidence of postoperative pain following single visit endodontics in vital and non-vital teeth: An in vivo study. Contemporary Clinical Dentistry 4(3): p 295-302, Jul–Sep 2013. | DOI: 10.4103/0976-237X.118352
56. Kane, A. W., Toure, B., Sarr, M., & Faye, B. (2000). Pain in intracanal treatment. A clinical study apropos of 150 cases. Odonto-stomatologie Tropicale= Tropical Dental Journal, 23(90), 5-10.
57. Restrepo-Restrepo, F. A., Cañas-Jiménez, S. J., Romero-Albarracín, R. D., Villa-Machado, P. A., Pérez-Cano, M. I., & Tobón-Arroyave, S. I. (2019). Prognosis of root canal treatment in teeth with preoperative apical periodontitis: a study with cone-beam computed tomography and digital periapical radiography. International endodontic journal, 52(11), 1533-1546. doi: 10.1111/iej.13168
58. Giampiero Rossi-Fedele, Yuan-Ling Ng. Effectiveness of root canal treatment for vital pulps compared with necrotic pulps in the presence or absence of signs of periradicular pathosis: A systematic review and meta-analysis. Int Endod J. 2022 Sep 15. doi: 10.1111/iej.13833.
59. DiRenzo, A., Gresla, T., Johnson, B. R., Rogers, M., Tucker, D., & BeGole, E. A. (2002). Postoperative pain after 1-and 2-visit root canal therapy. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 93(5), 605-610.
60. Edward M. O'Keefe. Pain in endodontic therapy: preliminary study. Journal of Endodontics. Volume 2, Issue 10, October 1976, Pages 315-319

61. Young-Eun Jang. Influence of Preoperative Mechanical Allodynia on Predicting Postoperative Pain after Root Canal Treatment: A Prospective Clinical Study. Journal of Endodontics. Volume 47, Issue 5, p770-778.e1, May 2021
62. Diogenes A., Henry M.A. Pain pathways and mechanisms of the pulpo-dentin complex. In: Hargreaves K.M., Goodis H.E., Tay F.R., editors. Seltzer and Bender's Dental Pulp.2nd ed. Quintessence; Hamilton, NY, USA: 2012. pp. 159–184.
63. Sundaramurthy, J. L., Natanasabapathy, V., Mahendran, K., Narasimhan, S., Raghu, S., Cherian, A. R., ... & Krithikadatta, J. (2023). Efficiency of Immediate and Controlled Release of Aceclofenac on Post-instrumentation Pain in Root Canal Treatment–A Triple Blind Randomized Controlled Trial. European Endodontic Journal, 8(2), 125-132. doi: 10.14744/eej.2022.40469.
64. Genet, J. M., Wesselink, P. R., & Van Velzen, S. T. (1986). The incidence of preoperative and postoperative pain in endodontic therapy. International endodontic journal, 19(5), 221-229. https://doi.org/10.1111/j.1365-2591.1986.tb00482.
65. M Helft, B Marshak. Split root: a common cause of undiagnosed or misdiagnosed pain. Quintessence Int Dent Dig. 1981 Oct;12(10):1031-6.
66. Testori, T., Badino, M., & Castagnola, M. (1993). Vertical root fractures in endodontically treated teeth: a clinical survey of 36 cases. Journal of Endodontics, 19(2), 87-90. doi: 10.1016/S0099-2399(06)81202-1.
67. Olivieri, J. G., Elmsmari, F., Miró, Q., Ruiz, X. F., Krell, K. V., García-Font, M., & Durán-Sindreu, F. (2020). Outcome and survival of endodontically treated cracked posterior permanent teeth: a systematic review and meta-analysis. Journal of Endodontics, 46(4), 455-463. doi: 10.1016/j.joen.2020.01.006
68. B Heling, I Heling. Endodontic procedures must never be performed without the rubber dam. OralSurg Oral Med Oral Pathol. 1977 Mar;43(3):464-6. doi: 10.1016/0030-4220(77)90334-6.
69. Glickman GN, Vogt MW. Preparation for treatment. In: Harg-reaves KM, Cohen SC, eds. Cohen's Pathways of the Pulp. 10thedn. Mosby, 2011:88–123.
70. P N R Nair. Microbial status of apical root canal system of human mandibular first molars with primary apical periodontitis after "one-visit" endodontic treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Feb;99(2):231-52. doi: 10.1016/j.tripleo.2004.10.005.
71. Chiconelli, C. P. C., Gabardo, M. C. L., Faria, M. I. A., & Olandoski, M. (2014). Prevalence of Pain after Endodontic Treatment. Brazilian Research in Pediatric Dentistry and Integrated Clinic, 14(3), 249-257.
72. Vera, J., Siqueira Jr, J. F., Ricucci, D., Loghin, S., Fernández, N., Flores, B., & Cruz, A. G. (2012). One-versus two-visit endodontic treatment of teeth with apical periodontitis: a histobacteriologic study. Journal of Endodontics, 38(8), 1040-1052. doi: 10.1016/j.joen.2012.04.010
73. Roane, J. B., Dryden, J. A., & Grimes, E. W. (1983). Incidence of postoperative pain after single-and multiple-visit endodontic procedures. Oral Surgery, Oral Medicine, Oral Pathology, 55(1), 68-72.
74. Risso, P. D. A., Cunha, A. J. L. A., Araujo, M. C. P., & Luiz, R. R. (2008). Postobturation pain and associated factors in adolescent patients undergoing one-and two-visit root canal treatment. Journal of Dentistry, 36(11), 928-934.
75. Z.S.M. Albashaireh, A.S. Alnegrish. Post obturation pain after single- and multiple-visit endodontic therapy. A prospective study. Journal of Dentistry. Volume 26, Issue 3, March 1998, Pages 227-232.
76. Figini, L., Lodi, G., Gorni, F., & Gagliani, M. (2008). Single versus multiple visits for endodontic treatment of permanent teeth: a Cochrane systematic review. Journal of Endodontics, 34(9), 1041-1047. doi: 10.1016/j.joen.2008.06.009
77. Iqbal A. The Factors Responsible for Endodontic Treatment Failure in the Permanent Dentitions of the Patients Reported to the College of Dentistry, the University of Aljouf, Kingdom of Saudi Arabia.J Clin of Diagn Res.2016; 10(5): ZC146-ZC148.
78. Pamboo, J., Hans, M. K., Kumaraswamy, B. N., Chander, S., & Bhaskaran, S. (2014). Incidence and factors associated with flare-ups in a post graduate programme in the Indian population. Journal of Clinical and Experimental Dentistry, 6(5), e514–e519.
79. Rao, K. N., Kandaswamy, R., Umashetty, G., Rathore, V. P. S., Hotkar, C., & Patil, B. S. (2014). Post-Obturation pain following one-visit and two-visit root canal treatment in necrotic anterior teeth. Journal of international oral health: JIOH, 6(2), 28-32.
80. Su, Y., Wang, C., & Ye, L. (2011). Healing rate and post-obturation pain of single-versus multiple-visit endodontic treatment for infected root canals: a systematic review. Journal of Endodontics, 37(2), 125-132.
81. Silva EJ, Menaged K, Ajuz N, Monteiro MR, CoutinhoFilho Tde S. Postoperative pain after foraminal enlargement in anterior teeth with necrosis and apical periodontitis: a prospective and randomized clinical trial. J Endod 2013; 39:173-6.
82. Nitzan, D. W., Stabholz, A., & Azaz, B. (1983). Concepts of accidental overfilling and over-instrumentation in the mandibular canal during root canal treatment. Journal of Endodontics, 9(2), 81-85.
83. Marina Fernandes, Ida de Ataide. Nonsurgical management of periapical lesions. J Conserv Dent. 2010 Oct;13(4):240-5. doi: 10.4103/0972-0707.73384

84. Tinaz AC, Alacam T, Uzun O, Maden M, Kayaouglu G. The effect of disruption of apical constriction on periapical extrusion. J Endod 2005; 31:533-5
85. Alothmani OS, Friedlander LT, Monteith BD, Chandler NP. Influence of clinical experience on the radiographic determination of endodontic working length. Int Endod J 2012; 46:211-6.
86. Weine FS. Endodontic therapy. 5th ed. St. Louis: Morsby; 1996. p. 243-75
87. David Green Stereomicroscopic study of 700 root apices of maxillary and mandibular posterior teeth. Oral Surgery, Oral Medicine, Oral Pathology Volume 13, Issue 6, June 1960, Pages 728-733
88. Basil Yousif Alamassi. Endodontic Postoperative Pain: Etiology and Related Factors. International Journal of Dental Sciences and Research. Vol. 5, No. 2, 2017, pp 13-21. doi: 10.12691/ijdsr-5-2-1
89. Wu MK, Wesselink PR, Walton RE. Apical terminus location of root canal treatment procedures. Oral Surg Oral Med Oral Pathol 2000; 89:99-103.
90. Arias A, Azabal M, Hidalgo JJ, de la Macorra JC. Relationship between post endodontic pain, tooth diagnostic factors, and apical patency J Endod 2009;35:189-92
91. Ashraf ElAyouti. Frequency of Overinstrumentation with an Acceptable Radiographic Working Length. Journal of Endodontics. Volume 27, Issue 1, P49-52, January 2001
92. Mohammadi Z, Jafarzadeh H. Establishing Apical Patency: To be or not to be? J Contemp Dent Pract. 2017; 18:326-329.
93. Shubham, S., Nepal, M., Mishra, R., & Dutta, K. (2021). Influence of maintaining apical patency in post-endodontic pain. BMC Oral Health, 21(1), 284. https://doi.org/10.1186/s12903-021-01632-x
94. E. Yaylali, S. Kurnaz, Y.M. Tunca. Maintaining Apical Patency Does Not Increase Postoperative Pain in Molars with Necrotic Pulp and Apical Periodontitis: A Randomized Controlled Trial. J. Endod., 44 (2018), pp. 335-340.
95. Topcuoglu HS, Duzgun S, Akpek F, Topcuoglu G, Aktı A. Influence of a glide path on apical extrusion of debris during canal preparation using single-file systems in curved canals. Int Endod J. 2016 Jun; 49(6): 599-603.
96. Topçuoğlu, H. S., Üstün, Y., Akpek, F., Aktı, A., & Topçuoğlu, G. (2016). Effect of coronal flaring on apical extrusion of debris during root canal instrumentation using single-file systems. International endodontic journal, 49(9), 884-889. doi: 10.1111/iej.12520
97. Borges, Á. H., Pereira, T. M., Porto, A. N., de Araújo Estrela, C. R., Pedro, F. L. M., Aranha, A. M. F., & Guedes, O. A. (2016). The influence of cervical preflaring on the amount of apically extruded debris after root canal preparation using different instrumentation systems. Journal of Endodontics, 42(3), 465-469.
98. Xi Wei. The effect of root canal preparation with nickel-titanium rotary instruments in reducing post-operative pain. Hua Xi Kou Qiang Yi Xue Za Zhi. 2003 Jun;21(3):202-4
99. Sun, C., Sun, J., Tan, M., Hu, B., Gao, X., & Song, J. (2018). Pain after root canal treatment with different instruments: a systematic review and meta-analysis. Oral diseases, 24(6), 908-919. doi: 10.1111/odi.12854.
100. Arias, A., De La Macorra, J. C., Azabal, M., Hidalgo, J. J., & Peters, O. A. (2015). Prospective case-controlled clinical study of post-endodontic pain after rotary root canal preparation performed by a single operator. Journal of Dentistry, 43(3), 389-395. doi: 10.1016/j.jdent.2014.07.008.
101. Silva, E. A. B., Guimaraes, L. S., Küchler, E. C., Antunes, L. A. A., & Antunes, L. S. (2017). Evaluation of effect of foraminal enlargement of necrotic teeth on postoperative symptoms: a systematic review and meta-analysis. Journal of Endodontics, 43(12), 1969-1977. doi: 10.1016/j.joen.2017.07.014
102. Nair, P.N.R. On the causes of persistent apical periodontitis: a review. International Endodontic Journal, 2006, 39: 249-281. https://doi.org/10.1111/j.1365-2591.2006.01099.x
103. Simon JHS, Chimenti Z, Mintz G. Clinical significance of the pulse granuloma. Journal of Endodontics 1982 8, 116– 9
104. King OH (1978) 'Giant cell hyaline angiopathy': pulse granuloma by another name? Presented at the 32nd Annual Meeting of the American Academy of Oral Pathologists, Fort Lauderdale.
105. Knoblich R. Pulmonary granulomatosis caused by vegetable particles. So-called lentil pulse granuloma. American Review of Respiratory Diseases 1969 99, 380– 9.
106. John D Regan, Alex A P Fleury. Irrigants in non-surgical endodontic treatment. J Ir Dent Assoc. 2006 Autumn;52(2):84-92.
107. James D. Johnson and Natasha M. Flake. Chapter 5 Impact of Root Canal Disinfection on Treatment Outcome. Pocket Dentistry
108. George G. Stewart. A Scanning Electron Microscopic Study of the Cleansing Effectiveness of Three Irrigating Modalities on the Tubular Structure of Dentin. Journal Of Endodontics Vol. 24, No. 7, July 1998
109. Zahed Mohammadi. Effects Of Root Canal Irrigants on The Planktonic Form of Enterococcus Faecalis: A Review. Niger J Med 2015 Jul-Sep;24(3):261-7.
110. Kaplan, T., Kaplan, S.S. & Sezgin, G.P. The effect of different irrigation and disinfection methods on postoperative pain in mandibular molars: a randomized clinical trial. BMC Oral Health 22, 601 (2022). https://doi.org/10.1186/s12903-022-02651-

111. Chalub, L. O., Nunes, G. P., Ferrisse, T. M., Strazzi-Sahyon, H. B., Dos Santos, P. H., Gomes-Filho, J. E., ... & Sivieri-Araujo, G. (2022). Postoperative pain in root canal treatment with ultrasonic versus conventional irrigation: a systematic review and meta-analysis of randomized controlled trials. Clinical Oral Investigations, 26(4), 3343-3356. doi: 10.1007/s00784-022-04386-0
112. Ruksakiet, K., Hanák, L., Farkas, N., Hegyi, P., Sadaeng, W., Czumbel, L. M., ... & Lohinai, Z. (2020). Antimicrobial efficacy of chlorhexidine and sodium hypochlorite in root canal disinfection: a systematic review and meta-analysis of randomized controlled trials. Journal of endodontics, 46(8), 1032-1041.
113. Bashetty Kusum, Hegde Jayshree. Comparison of 2% chlorhexidine and 5.25% sodium hypochlorite irrigating solutions on postoperative pain: A randomized clinical trial. Indian Journal of Dental Research. Year: 2010 | Volume: 21 | Issue Number: 4 | Page: 523-527
114. Alkahtani, A., Al Khudhairi, T.D. & Anil, S. A comparative study of the debridement efficacy and apical extrusion of dynamic and passive root canal irrigation systems. BMC Oral Health 14, 12 (2014). https://doi.org/10.1186/1472-6831-14-12
115. Hulsmann M., Han W. Complication during root canal irrigation-Literature Review and Case Reports. Int endod J 2000; 33: 186-193
116. Ehrich DG, Brian JD, Walker WA. Sodium Hypochlorite accident: inadvertent injection into the maxillary sinus. J Endod 1993; 19: 180-2
117. Estrela C., Estrela CRA. Mechanism of action of Sodium Hypochlorite. Braz Dent J 2002; 13:113-117
118. Jose F Siqueira Jr. Clinical outcome of the endodontic treatment of teeth with apical periodontitis using an antimicrobial protocol. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 Nov;106(5):757-62. doi: 10.1016/j.tripleo.2008.06.007
119. B. S. Chong, T. R. Pitt Ford. The role of intracanal medication in root canal treatment. International Endodontic Journal. March 1992 https://doi.org/10.1111/j.1365-2591.1992.tb00743.
120. Siqueira Jr, J. F., Rôças, I. N., Favieri, A., Machado, A. G., Gahyva, S. M., Oliveira, J. C., & Abad, E. C. (2002). Incidence of postoperative pain after intracanal procedures based on an antimicrobial strategy. Journal of Endodontics, 28(6), 457-460.
121. Khan, A. M., Gangoo, I. K. A., Ali, N. A., Khan, M., Javed, M. Q., AlAttas, M. H., ... & Yahya, R. S. A. (2023). The effect of calcium hydroxide, triple antibiotic paste and chlorhexidine on pain in teeth with symptomatic apical periodontitis: a randomised controlled trial. International Journal of Environmental Research and Public Health, 20(4), 3091.
122. Abouelenien SS, Ibrahim SM, Shaker OG and Ahmed GM. Evaluation of postoperative pain in infected root canals after using double antibiotic paste versus calcium hydroxide as intra-canal medication: A randomized controlled trial F1000Research 2018, 7:1768 (https://doi.org/10.12688/f1000research.16820.1)
123. Vatankhah, M., Khosravi, K., Zargar, N., Shirvani, A., Nekoofar, M. H., & Dianat, O. (2022). Antibacterial efficacy of antibiotic pastes versus calcium hydroxide intracanal dressing: A systematic review and meta-analysis of ex vivo studies. Journal of Conservative Dentistry: JCD, 25(5), 463–480.
124. E H Ehrmann 1, H H Messer, G G Adams. The relationship of intracanal medicaments to postoperative pain in endodontics. Int Endod J. 2003 Dec;36(12):868-75. doi: 10.1111/j.1365-2591.2003.00735.
125. Barthel, C. R., Zimmer, S., West, G., & Roulet, J. F. (2000). Bacterial leakage in obturated root canals following the use of different intracanal medicaments. Dental Traumatology, 16(6), 282-286. doi: 10.1034/j.1600-9657.2000.016006282. x.
126. Nobuyuki Kawashima. Root canal medicaments. Int Dent J.2009 Feb;59(1):5-11.
127. Anjaneyulu K, Nivedhitha Malli Sureshbabu. Influence of calcium hydroxide on the post-treatment pain in Endodontics: A systematic review. Journal of Conservative Dentistry. Year: 2014 | Volume: 17 | Issue Number: 3 | Page: 200-207
128. José F Siqueira Jr 1, Tatiana Guimarães-Pinto, Isabela N Rôças. Effects of chemomechanical preparation with 2.5% sodium hypochlorite and intracanal medication with calcium hydroxide on cultivable bacteria in infected root canals. J Endod. 2007 Jul;33(7):800-5. doi: 10.1016/j.joen.2006.11.023.
129. Ashima Nadar. A comparative evaluation of calcium ion release and pH change using calcium hydroxide nanoparticles as intracanal medicament with different vehicles - An in vitro study. J Conserv Dent. 2023 Jan-Feb;26(1):47-51. doi: 10.4103/jcd.jcd_387_22.
130. White EW. Paper point in mental foramen. Oral Surgery, Oral Medicine and Oral Pathology 1968. 25, 630– 2.
131. Sedgley & Messer 1993 Sedgley CM, Messer H (1993) Long-term retention of a paper-point in the periapical tissues: a case report. Endodontics and Dental Traumatology 9, 120– 3.
132. Kaur A, Shah N, Logani A, Mishra N. Biotoxicity of commonly used root canal sealers: A meta-analysis. J Conserv Dent. 2015 Mar-Apr;18(2):83-8. doi: 10.4103/0972-0707.153054. PMID: 25829682; PMCID: PMC4379664.

133. Coşar, M., Kandemir Demirci, G., & Çalışkan, M. K. (2023). The effect of two different root canal sealers on treatment outcome and post-obturation pain in single-visit root canal treatment: A prospective randomized clinical trial. International Endodontic Journal, 56(3), 318-330.
134. Anita Aminoshariae, James C. Kulild. The impact of sealer extrusion on endodontic outcome: A systematic review with meta-analysis. Australian Endodontic Journal. 26 August 2019 https://doi.org/10.1111/aej.12370.
135. Seron, M. A., Nunes, G. P., Ferrisse, T. M., Strazzi-Sahyon, H. B., Victorino, F. R., Dos Santos, P. H., ... & Sivieri-Araujo, G. (2023). Postoperative pain after root canal filling with bioceramic sealers: a systematic review and meta-analysis of randomized clinical trials. Odontology, 1-20. doi: 10.1007/s10266-023-00830-z
136. Emma Carr, Andrew MacInnes. Do resin-based sealers increase post-operative pain following root-canal treatment? Evid Based Dent. 2022 Sep;23(3):114-115. doi: 10.1038/s41432-022-0804-3.
137. Monteiro CM, Martins AC, Reis A, de Geus JL. Effect of endodontic sealer on postoperative pain: a network meta-analysis. Restor Dent Endod. 2023 Feb;48(1): e5. https://doi.org/10.5395/rde.2023.48.e5
138. Scarano, A., Di Carlo, F., Quaranta, A., & Piattelli, A. (2007). Injury of the inferior alveolar nerve after overfilling of the root canal with endodontic cement: a case report. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 104(1), e56-e59. doi: 10.1016/j.tripleo.2007.01.036.
139. Dalopoulou, A., Economides, N., & Evangelidis, V. (2017). Extrusion of root canal sealer in periapical tissues: Report of two cases with different treatment management and literature review. Balkan Journal of Dental Medicine, 21(1), 12-18.
140. Harrison, J. W., Baumgartner, J. C., & Svec, T. A. (1983). Incidence of pain associated with clinical factors during and after root canal therapy. Part 2. Postobturation pain. Journal of Endodontics, 9(10), 434-438.
141. Martín-González, J., Echevarría-Pérez, M., Sánchez-Domínguez, B., Tarilonte-Delgado, M. L., Castellanos-Cosano, L., López-Frías, F. J., & Segura-Egea, J. J. (2012). Influence of root canal instrumentation and obturation techniques on intra-operative pain during endodontic therapy. Medicina Oral, Patología Oral y Cirugía Bucal, 17(5), e912–e918.
142. Yu, Y. H., Kushnir, L., Kohli, M., & Karabucak, B. (2021). 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. Clinical Oral Investigations, 25, 5033-5042.
143. Alonso-Ezpeleta, L. O., Gasco-Garcia, C., Castellanos-Cosano, L., Martín-González, J., López-Frías, F. J., & Segura-Egea, J. J. (2012). Postoperative pain after one-visit root-canal treatment on teeth with vital pulps: comparison of three different obturation techniques. Medicina oral, patologia oral y cirugia bucal, 17(4), e721–e727.
144. Mello, F. W., Miguel, A. F. P., Ribeiro, D. M., Pasternak, B., Porporatti, A. L., Flores-Mir, C., ... & Dutra-Horstmann, K. L. (2019). The influence of apical extent of root canal obturation on endodontic therapy outcome: a systematic review. Clinical oral investigations, 23, 2005-2019.
145. Ricucci, Langeland. Apical limit of root canal instrumentation and obturation, part 2. A histological study. International Endodontic Journal. 04 January 2002 https://doi.org/10.1046/j.1365-2591.1998.00183.x
146. Seltzer S, Bender IB, Turkenkopf S (1963) Factors affecting successful repair after root canal treatment. Journal of the American Dental Association 67, 651– 62.
147. Rao, S., Nilker, V., Telikapalli, M., Gala, K., & Nilkar, V. (2023). Incidence of Endodontic Failure Cases in the Department of Conservative Dentistry and Endodontics, DY Patil School of Dentistry, Navi Mumbai. Cureus, 15(5), e38841. DOI 10.7759/cureus.38841
148. Azhar Iqbal, The Factors Responsible for Endodontic Treatment Failure in the Permanent Dentitions of the Patients Reported to the College of Dentistry, the University of Aljouf, Kingdom of Saudi Arabia. Journal of Clinical and Diagnostic Research. 2016 May, Vol-10(5): ZC146-ZC148
149. Iftikhar Akbar. Radiographic study of the problems and failures of endodontic treatment. Int J Health Sci (Qassim). 2015 Apr;9(2):111-8.
150. Durre Sadaf, Muhammad Zubair Ahmad. Factors Associated with Postoperative Pain in Endodontic Therapy. Int J Biomed Sci. 2014 Dec; 10(4): 243–247.
151. Mohammed Adam. 'Combined endo-perio lesions' - what is the best treatment? Review Evid Based Dent. 2021 Dec;22(4):158-159.
152. Raldi, D. P., Mello, I., Márcia Habitante, S., Lage-Marques, J. L., & Coil, J. (2009). Treatment options for teeth with open apices and apical periodontitis. Journal of the Canadian Dental Association, 75(8). www.cda-adc.ca/jcda
153. Siqueira JF Jr, Rôças IN (2004) Polymerase chain reaction-based analysis of microorganisms associated with failed endodontic treatment. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics 97, 85– 94
154. Nair PNR (1987) Light and electron microscopic studies of root canal flora and periapical lesions. Journal of Endodontics 13, 29– 39.

155. L M Lin, J E Skribner, P Gaengler. Factors associated with endodontic treatment failures. J Endod. 1992 Dec;18(12):625-7. doi: 10.1016/S0099-2399(06)81335
156. Shovelton DS (1964) The presence and distribution of micro-organisms within non-vital teeth. British Dental Journal 117, 101– 7
157. Love RM, McMillan MD, Jenkinson HF (1997) Invasion of dentinal tubules by oral Streptococci is associated with collagen regeneration mediated by the antigen I/II family of polypeptides. Infection and Immunity 65, 5157– 64
158. M-K Wu, P M H Dummer, P R Wesselink. Consequences of and strategies to deal with residual post-treatment root canal infection. Int Endod J. 2006 May;39(5):343-56. doi: 10.1111/j.1365-2591.2006.01092. x.
159. A Bystrom, G Sundqvist. Bacteriologic evaluation of the efficacy of mechanical root canal instrumentation in endodontic therapy. Scand J Dent Res.1981 Aug;89(4):321-8. doi: 10.1111/j.1600-0722. 1981.tb01689. x.
160. J F Siqueira Jr. Strategies to treat infected root canals. J Calif Dent Assoc. 2001 Dec;29(12):825-37.
161. H Martin. Cleanliness, disinfection, and sterilization of the root canal. Curr Opin Dent. 1991 Dec;1(6):734-6.
162. Siqueira JR, Rocas IN, Souta R, Uzeda M, Colombo AP. Microbiological evaluation of acute periradicular abscesses by DNA-DNA hybridizaion. Oral Surg Oral Med Oral Pathol 2001; 92: 451-7.
163. Luis Eduardo Chávez de Paz Villanueva. Fusobacterium nucleatum in endodontic flare-ups. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology. Volume 93, Issue 2, P179-183, February 2002.
164. Stuart, C. H., Schwartz, S. A., Beeson, T. J., & Owatz, C. B. (2006). Enterococcus faecalis: its role in root canal treatment failure and current concepts in retreatment. Journal of Endodontics, 32(2), 93-98. doi: 10.1016/j.joen.2005.10.049.
165. Sundqvist G, Figdor D (1998) Endodontic treatment of apical periodontitis. In: D Orstavik, TR Pitt Ford, eds. Essential Endodontology. Oxford, UK: Blackwell, pp. 242– 77.
166. Niu, W. D., Song, Q. Y., Wang, L. N., Zheng, J. B., Shi, C., Li, J. Y., & Zhou, X. D. (2010). Analysis of relationship between the detection of Enterococcus faecalis in post-treatment endodontic disease and clinical symptom or sign. Hua xi kou Qiang yi xue za zhi= Huaxi Kouqiang Yixue Zazhi= West China Journal of Stomatology, 28(5), 535-538.
167. Fouad AF, Zerella J, Barry J, Sapangberg LS (2005) Molecular detection of Enterococcus species in root canals of therapy-resistant endodontic infections. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology 99, 112– 8
168. Figdor D, Davies JK, Sundqvist G (2003) Starvation survival, growth and recovery of Enterococcus faecalis in human serum. Oral Microbiology and Immunology 18, 234– 9.
169. Barbosa-Ribeiro, M., Arruda-Vasconcelos, R., Louzada, L. M., Dos Santos, D. G., Andreote, F. D., & Gomes, B. P. (2021). Microbiological analysis of endodontically treated teeth with apical periodontitis before and after endodontic retreatment. Clinical oral investigations, 25, 2017-2027. doi: 10.1007/s00784-020-03510-2.
170. Torabinejad M., Keltering JD, McGrav JC, Cummings RR, Dwyer TG, Tobias TS. Factors associated with endodontic interappointment emergencies of teeth with necrotic pulps. J Endod 1988; 14: 261-6
171. Robert J. Matusow. Acute pulpal-alveolar cellulitis syndrome IV. Exacerbations during endodontic treatment: A clinical study of specific microbial isolates and their etiologic role: Part 1. Oral Surgery, Oral Medicine, Oral Pathology. Volume 61, Issue 1, January 1986, Pages 90-95
172. Kakehashi S, Stanley HR, Fitzgerald RJ (1965) The effects of surgical exposures of dental pulps in germ-free and conventional laboratory rats. Oral Surgery, Oral Medicine and Oral Pathology 20, 340– 9.
173. Machado, F. P., Khoury, R. D., Toia, C. C., Flores Orozco, E. I., de Oliveira, F. E., de Oliveira, L. D., ... & Valera, M. C. (2020). Primary versus post-treatment apical periodontitis: microbial composition, lipopolysaccharides and lipoteichoic acid levels, signs and symptoms. Clinical oral investigations, 24, 3169-3179.
174. Seltzer S, Naidorf IJ. Flare - ups in Endodontics: I. Etiological factors. J Endod 2004; 30:476-81.
175. Gunnar Dahlén. Culture-Based Analysis of Endodontic Infections. Endodontic Microbiology, Second Edition. Chap 4. February 2017 https://doi.org/10.1002/9781119080343.ch4
176. Sjögren, U., Figdor, D., Persson, S., & Sundqvist, G. (1997). Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. International endodontic journal, 30(5), 297-306.
177. Waltimo TMT, Siren EK, Torkko HLK, Olsen I, Haapasalo MPP (1997) Fungi in therapy-resistant apical periodontitis. International Endodontic Journal 30, 96– 101.
178. Nair, P. R., Sjögren, U., Krey, G., Kahnberg, K. E., & Sundqvist, G. (1990). Intraradicular bacteria and fungi in root-filled, asymptomatic human teeth with therapy-resistant periapical lesions: a long-term light and electron microscopic follow-up study. Journal of endodontics, 16(12), 580-588.
179. Naoum HJ, Chandler NP. Temporization for endodontics. Int Endod J 2002; 35:964-78

180. Cohen S, Burns RC. Pathway of the pulp, Eighth Edition 2002:61-65.
181. Kapsimalis P, Garrington GE (1968) Actinomycosis of the periapical tissues. Oral Surgery, Oral Medicine and Oral Pathology 26, 374– 80
182. Sundqvist G, Reuterving CO (1980) Isolation of Actinomyces israelii from periapical lesion. Journal of Endodontics 6, 602– 6
183. Sabeti M, simon JH, SlootsJ. Cytomegalovirus and Epstein-Barr virus are associated with symptomatic periapical pathosis. Oral Microbiol Immunol 2003; 18: 327-8.
184. Slots J, Sabeti M, Simon J. Herpesviruses in periapical pathosis: An etiopathogenic relationship. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 96: 327-31.
185. Fabricius, L., Dahlén, G., Sundqvist, G., Happonen, R. P., & Möller, Å. J. (2006). Influence of residual bacteria on periapical tissue healing after chemomechanical treatment and root filling of experimentally infected monkey teeth. European journal of oral sciences, 114(4), 278-285. doi: 10.1111/j.1600-0722.2006.00380. x.
186. Lin, L. M., Pascon, E. A., Skribner, J., Gängler, P., & Langeland, K. (1991). Clinical, radiographic, and histologic study of endodontic treatment failures. Oral surgery, oral medicine, oral pathology, 71(5), 603-611. doi: 10.1016/0030-4220(91)90371-i.
187. Frank: Resorption, Perforation and fracture. Dental Clinic North America 1974: 18: 465-487.
188. Gbadebo, S. O. (2016). Endodontic flare up: incidence and association of possible risk factors. African Journal of Medicine and Medical Sciences, 45(2), 207-212.
189. Mashyakhy, M., Hadi, F. A., Alhazmi, H. A., Alfaifi, R. A., Alabsi, F. S., Bajawi, H., ... & AbuMelha, A. (2021). Prevalence of missed canals and their association with apical periodontitis in posterior endodontically treated teeth: a CBCT study. International Journal of Dentistry, 2021. Article ID 9962429, 6 pages, 2021. https://doi.org/10.1155/2021/9962429
190. Alnowailaty Y, Alghamdi F (June 03, 2022) Prevalence of Endodontically Treated Premolars and Molars with Untreated Canals and Their Association with Apical Periodontitis Using Cone-Beam Computed Tomography. Cureus 14(6): e25619. doi:10.7759/cureus.25619
191. Pogrel MA. Damage to the inferior alveolar nerve as the result of root canal therapy. JADA, 2007; 138:65-69.
192. Conrad SM. Neurosensory disturbances as a result of chemical injury to the inferior alveolar nerve. J Oral Maxillofac Surg, 2001; 13:255-263.
193. P, Gaudy JF. Labiomandibular paraesthesia caused by endodontic treatment: an anatomic and clinical study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2006; 102:47-59.
194. Oseoglou BG, Tanrikulu S, Subay RK, Sencer S. Anesthesia following overfilling of a root canal sealer into the mandibular canal: A case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2006; 101:803-806
195. Nair PN. Non-microbial etiology: foreign body reaction maintaining post-treatment apical periodontitis. Endod Topics, 2003; 6:114-134
196. Spielman A, Gutman D, Laufer D. Anesthesia following endodontic overfilling with AH26. Oral Surg Oral Med Oral Pathol, 1981; 52:554-556.
197. Khongkhunthian P, Reichart PA. Aspergillosis of the maxillary sinus as a complication of overfilling root canal material into the sinus: Report of two cases. J Endod, 2001; 27:476-478. 13.
198. Beck-Mannagetta J, Necek D. Radiologic findings in aspergillosis of the maxillary sinus. Oral Surg Oral Med Oral Pathol Oral Radio Endod, 1986; 62:345-349
199. Ahlgren FK, Johannessen AC, Hellem S. Displaced calcium hydroxide paste causing inferior alveolar nerve paraesthesia: report of a case. Oral Surg Oral Med Oral Pathol Radiol Endod, 2003; 96;734-737.
200. Lin, L. M., Rosenberg, P. A., & Lin, J. (2005). Do procedural errors cause endodontic treatment failure? The Journal of the American Dental Association, 136(2), 187-193. quiz 231. doi: 10.14219/jada.archive.2005.0140.
201. Waqas Yousuf, Moiz Khan, Hasan Mehdi, "Endodontic Procedural Errors: Frequency, Type of Error, and the Most Frequently Treated Tooth", International Journal of Dentistry, vol. 2015, Article ID 673914, 7 pages, 2015. https://doi.org/10.1155/2015/673914
202. Talal Al-Nahlawi. Dentists' Knowledge, Attitude and Practice of Root Canal Treatment Procedure: Survey-based Research. J Contemp Dent Pract. 2019 Mar 1;20(3):347-354.
203. Michael M Hoen, Frank E Pink. Contemporary endodontic retreatments: an analysis based on clinical treatment findings. J Endod. 2002 Dec;28(12):834-6. doi: 10.1097/00004770-200212000-00010.
204. Parirokh, M., Rekabi, A. R., Ashouri, R., Nakhaee, N., Abbott, P. V., & Gorjestani, H. (2013). Effect of occlusal reduction on postoperative pain in teeth with irreversible pulpitis and mild tenderness to percussion. Journal of Endodontics, 39(1), 1-5. doi: 10.1016/j.joen.2012.08.008.
205. Rosenberg, P. A., Babick, P. J., Schertzer, L., & Leung, A. (1998). The effect of occlusal reduction on pain after endodontic instrumentation. Journal of Endodontics, 24(7), 492-496. doi: 10.1016/S0099-2399(98)80054.
206. Nguyen, D., Nagendrababu, V., Pulikkotil, S. J., & Rossi-Fedele, G. (2020). Effect of occlusal reduction on postendodontic pain: A systematic review and meta-analysis of randomised clinical

trials. Australian Endodontic Journal, 46(2), 282-294. doi: 10.1111/aej.12380.
207. Balevi, B. Managing post endodontic treatment pain by eliminating occlusal contacts. Evid Based Dent 20, 109–110 (2019). https://doi.org/10.1038/s41432-019-0055-0
208. Sayna Shamszadeh. Does occlusal reduction reduce post-endodontic pain? A systematic review and meta-analysis. J Oral Rehabil. 2020 Apr;47(4):528-535. doi: 10.1111/joor.12929.
209. Emara, R. S., Abou El Nasr, H. M., & El Boghdadi, R. M. (2019). Evaluation of postoperative pain intensity following occlusal reduction in teeth associated with symptomatic irreversible pulpitis and symptomatic apical periodontitis: a randomized clinical study. International endodontic journal, 52(3), 288-296. https://doi.org/10.1111/iej.13012
210. Smith, E. A., Marshall, J. G., Selph, S. S., Barker, D. R., & Sedgley, C. M. (2017). Nonsteroidal anti-inflammatory drugs for managing postoperative endodontic pain in patients who present with preoperative pain: a systematic review and meta-analysis. Journal of Endodontics, 43(1), 7-15. doi: 10.1016/j.joen.2016.09.010.
211. Nabi, S., Amin, K., Masoodi, A., Farooq, R., Purra, A. R., & Ahangar, F. A. (2018). Effect of preoperative ibuprofen in controlling postendodontic pain with and without low-level laser therapy in single visit endodontics: A randomized clinical study. Indian Journal of Dental Research, 29(1), 46-50. doi: 10.4103/ijdr.IJDR_327_15.
212. Elzaki, W. M., Abubakr, N. H., Ziada, H. M., & Ibrahim, Y. E. (2016). Double-blind randomized placebo-controlled clinical trial of efficiency of nonsteroidal anti-inflammatory drugs in the control of post-endodontic pain. Journal of Endodontics, 42(6), 835-842. doi: 10.1016/j.joen.2016.02.014.
213. Ong, C. K., Seymour, R. A., Lirk, P., & Merry, A. F. (2010). Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesthesia & Analgesia, 110(4), 1170-1179. doi: 10.1213/ANE.0b013e3181cf9281.
214. Zanjir, M., Sgro, A., Lighvan, N. L., Yarascavitch, C., Shah, P. S., da Costa, B. R., & Azarpazhooh, A. (2020). Efficacy and safety of postoperative medications in reducing pain after nonsurgical endodontic treatment: a systematic review and network meta-analysis. Journal of endodontics, 46(10), 1387-1402.
215. Kumar, G., Sangwan, P., & Tewari, S. (2021). Effect of premedication on postoperative pain after root canal therapy in patients with irreversible pulpitis: a systematic review and meta-analysis. Journal of Dental Anesthesia and Pain Medicine, 21(5), 397–411.
216. Shamszadeh, S., Shirvani, A., Eghbal, M. J., & Asgary, S. (2018). Efficacy of corticosteroids on postoperative endodontic pain: a systematic review and meta-analysis. Journal of Endodontics, 44(7), 1057-1065.
217. Milani, A. S., Froughreyhani, M., Taghiloo, H., Nouroloyouni, A., & Jafarabadi, M. A. (2022). The effect of antibiotic use on endodontic post-operative pain and flare-up rate: a systematic review with meta-analysis. Evidence-Based Dentistry, 1-9. https://doi.org/10.1038/s41432-021-0205-z
218. Anita Aminoshariae, James C Kulild. Evidence-based recommendations for antibiotic usage to treat endodontic infections and pain: A systematic review of randomized controlled trials. J Am Dent Assoc. 2016 Mar;147(3):186-91. doi: 10.1016/j.adaj.2015.11.002.
219. Contardo, L. U. C. A., Meneguzzi, E., Cadenaro, M. I. L. E. N. A., & Di Lenarda, R. (2005). Clinical evaluation of antibiotic prophylaxis before endodontic treatment of necrotic teeth. Minerva Stomatologica, 54(3), 153-160.
220. Lockhart, P. B., Tampi, M. P., Abt, E., Aminoshariae, A., Durkin, M. J., Fouad, A. F., ... & Carrasco-Labra, A. (2019). Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal-and periapical-related dental pain and intraoral swelling: A report from the American Dental Association. The Journal of the American Dental Association, 150(11), 906-921.
221. Fouad, A.F, Byrne, B.E, Diogenes, A.R, Sedgley, C.M AAE Guidance on the Use of Systemic Antibiotics in Endodontics, AAE Position Statement. 2017. Available online: www.aae.org/specialty/wp-content/uploads/sites/2/2017/06/aae_systemic-antibiotics.pdf
222. Segura-Egea. Antibiotics in Endodontics: a review. International EndodonticJournal50, 1169–84.
223. Fouad, A. F., Abbott, P. V., Tsilingaridis, G., Cohenca, N., Lauridsen, E., Bourguignon, C., ... & Levin, L. (2020). International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 2. Avulsion of permanent teeth. Dental traumatology, 36(4), 331-342. https://doi.org/10.1111/edt.12573.
224. Andersson L, Andreasen JO, & Day P. (2012) International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 2. Avulsion of permanent teeth. Dental Traumatology, 28, 88–96.
225. DiAngelis, A. J., Andreasen, J. O., Ebeleseder, K. A., Kenny, D. J., Trope, M., Sigurdsson, A., ... & Tsukiboshi, M. (2012). International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 1.

Fractures and luxations of permanent teeth. Dental Traumatology, 28(1), 2-12.
226. European Society of Endodontology (2006) Quality guidelines for endodontic treatment: consensus report of the European Society of Endodontology. International Endodontic Journal, 39, 921–30.
227. Agnihotry, A., Thompson, W., Fedorowicz, Z., van Zuuren, E. J., & Sprakel, J. (2019). Antibiotic use for irreversible pulpitis. Cochrane Database of Systematic Reviews, (5). https://doi.org/10.1002/14651858.CD004969.pub4
228. Bax R. Development of a twice daily dosing regimen of amoxicillin/clavulanate. International Journal of Antimicrobial Agents 2007 30(Suppl 2), S118–21
229. American Association of Endodontists (AAE) (1999) Prescription for the future: responsible use of antibiotics in endodontic therapy. AAE Endodontics Colleagues for Excel-lence1999,1–8).
230. Dar-Odeh, N. S., Abu-Hammad, O. A., Al-Omiri, M. K., Khraisat, A. S., & Shehabi, A. A. (2010). Antibiotic prescribing practices by dentists: a review. Therapeutics and clinical risk management, 6, 301-6.
231. Chen, Y.; Chen, X.L.; Zou, X.L.; Chen, S.Z.; Zou, J.; Wang, Y. Efficacy of low-level laser therapy in pain management after root canal treatment or retreatment: A systematic review. Lasers Med. Sci. 2019, 34, 1305–1316.
232. Guerreiro, M. Y. R., Monteiro, L. P. B., de Castro, R. F., Magno, M. B., Maia, L. C., & da Silva Brandão, J. M. (2021). Effect of low-level laser therapy on postoperative endodontic pain: An updated systematic review. Complementary Therapies in Medicine, 57, 102638.
233. Gupta, A., Aggarwal, V., Gurawa, A., Mehta, N., Abraham, D., Singh, A., ... & Chauhan, N. (2021). Effect of intracanal cryotherapy on postendodontic pain: a systematic review and meta-analysis of randomized controlled trials. Journal of Dental Anesthesia and Pain Medicine, 21(1), 15-27.
234. Sadaf, D.; Ahmad, M.Z.; Onakpoya, I.J. Effectiveness of Intracanal Cryotherapy in Root Canal Therapy: A Systematic Review and Meta-analysis of Randomized Clinical Trials. J. Endod. 2020, 46, 1811–1823
235. Monteiro, L.P.B.; Guerreiro, M.Y.R.; de Castro Valino, R.; Magno, M.B.; Maia, L.C.; da Silva Brandão, J.M. Effect of intracanal cryotherapy application on postoperative endodontic pain: A systematic review and meta-analysis. Clin. Oral Investig. 2021, 25,23–35
236. Akpinar KE, Kaya F. Effect of different clinical practices on postoperative pain in permanent mandibular molar teeth with symptomatic apical periodontitis: A randomized controlled clinical trial. Niger J Clin Pract 2021; 24:8-16.
237. Alonaizan, F.A.; AlFawaz, Y.F. Is phototherapy effective in the management of post-operative endodontic pain? A systematic review of randomized controlled clinical trials. Photodiagnosis Photodyn. Ther. 2019, 26, 53–58
238. Simon 1980 Incidence of periapical cysts in relation to the root canal. Journal of Endodontics 6, 845– 8.
239. Nair, P. N. R., Sjögren, U., Schumacher, E., & Sundqvist, G. (1993). Radicular cyst affecting a root-filled human tooth: a long-term post-treatment follow-up. International Endodontic Journal, 26(4), 225-233.
240. Neville B.W., Damm D.D., Allen C.M., Chi A.C. In: Oral and maxillofacial pathology. 4th ed. Elsevier; St. Louis: 2016. Pulpal and periapical disease; pp. 117–126.
241. Shear 1963 The histogenesis of dental cysts. Dental Practitioner 13, 238– 43.
242. Browne RM (1971) The origin of cholesterol in odontogenic cysts in man. Archives of Oral Biology 16, 107– 13
243. Nair, P. R., Sjögren, U., Figdor, D., & Sundqvist, G. (1999). Persistent periapical radiolucencies of root-filled human teeth, failed endodontic treatments, and periapical scars. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 87(5), 617-627.