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Review

The Novel Role of Solvents in Non-Surgical Endodontic Retreatment

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Abstract: Non-surgical endodontic retreatment is a reliable conservative option for managing post-treatment apical periodontitis. However, effective microbial control, based on the maximization of filling removal and disinfection protocols, is not yet predictable. Traditional gutta-percha solvents, which are indistinctively used for both the core and sealer filling materials, became obsolete due to unprecedented advances in endodontic technology. Nonetheless, microtomography, scanning electronic microscopy findings, and histobacteriological analysis tend to confirm the persistence of filling materials and the lack of association between root canal enlargement and superior disinfection. There is a controversy regarding the most suitable clinical protocols surrounding the shaping procedures and the supplementary disinfection steps. Based on the literature and the previous work of the team, the authors aimed to summarize the current knowledge regarding specific solvent formulations that target filling materials. Additionally, the advantage of an additional irrigation step to optimize disinfection was highlighted. This adjunctive procedure serves a dual role in the dissolution of filling materials, and in conferring an antibiofilm effect. Further research is needed to understand the novel contribution of these strategies upon clinical practice outcomes.

Keywords: endodontics; filling materials; gutta-percha; irrigating solutions; non-surgical endodontic retreatment; sealer; solvents

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1. Introduction

Non-surgical endodontic retreatment (NSER) is a conservative option for managing persistent apical periodontitis (AP) associated with root-filled teeth, or where a new disease has emerged after root canal filling. Its main objective is to reduce the interradicular bacterial load to levels that are compatible with periapical healing, relying on maximum filling removal, repreparation through the most complete and canal-centered shaping techniques, and disinfection protocols [1]. However, the current therapy still focuses on the main root canal.

Reducing old filling remnants is crucial, as they may harbor intraradicular biofilms, the main cause of post-treatment AP [2]. The relative difficulty of NSER is related to variables such as the design of the retreatment/instrumentation systems, the age and type of the root canal filling, and previous preparation errors, besides the complex root canal anatomy [3]. After regaining access to the apical foramen, chemo-mechanical preparation (repreparation) aims to further remove filling residues and disrupt persisting adhered biofilms. Current retreatment techniques include rotary files, ultrasonic instruments, heat, laser, hand files, and solvent solutions [3]. Although their combination is generally required, removing the bulk of the obturations has greatly improved with the development of nickel–titanium (NiTi) rotary systems. This improvement has led to clinicians rarely using solvents.

Two main strategies have been proposed to optimize disinfection before the new filling: (i) a further apical enlargement [4], with the risk of weakening the root structure; or

(ii) using adjunctive procedures, such as sonic/ultrasonic processes or recently developed finishing instruments, to activate the standard sodium hypochlorite (NaOCl) irrigating solution [5,6]. Laser and photoactivated therapies have also been mentioned, despite their inherent high costs [7,8]. The subsequent sealing and the remaining cervical and radicular dentin structure have also been considered to be factors of favorable outcomes [9,10]. However, the current state-of-art, which involves combining adequate mechanical shaping and activated antimicrobial irrigating solutions, namely NaOCl, is still not able to provide a predictable outcome for NSER. Furthermore, there is no evidence for an improvement in the periapical status of populations that are concomitant with the extensive advance in endodontic knowledge and research [10].

Following the evolution path of NiTi instruments, new engine-driven NiTi instruments, for purposes other than shaping, such as glide path preparation, retreatment, or irrigation enhancement, have emerged. The ProTaper retreatment (Dentsply Maillefer), the self-adjusting file, or the XP-endo Finisher (FKG Dentaire) are some elucidative examples [11]. On the other hand, recent investigations using proposals that are safer and as effective as chloroform, such as methyl ethyl ketone (MEK), ethyl acetate, and novel solvent mixtures (MEK/tetrachloroethylene (TCE) and MEK/orange oil (OOil)), have highlighted an additional role for endodontic solvents. There is no intention of promoting the use of solvents per se, but essentially the purpose is to uncover different paths for optimizing disinfection in retreatment procedures without neglecting all of the available options. Apart from filling dissolution, its antibiofilm efficacy, enhanced by agitation, opens new perspectives in the current retreatment disinfecting protocol [12–14]. Built on the literature search and the previous work of the team, one of the major goals was to identify and summarize new solvent proposals concerning their specificity, their moment of use, their enhancement through agitation and biocompatibility, their effects on dentin structure, and their antimicrobial/antibiofilm activity in NSER.

2. Evolution of Endodontic Solvent Compounds

Traditional gutta-percha solvents are chemical substances, usually organic, whose primary objective is the dissolution or softening of filling materials (particularly gutta-percha). Studies on the advantages of their use are not consensual [15]. Some authors have stated that solvents should only be used when the working length is hard to reach [16]. Eventual disadvantages have also been reported, such as slowing of the retreatment process due to a higher accumulation of filling material remnants [16,17]. On the other hand, the isolated use of mechanical instruments has been associated with several problems, including perforating roots and straightening canals, preventing their original shape from being preserved [3].

Chloroform is one of the most popular gold-standard gutta-percha solvents, with a long history in endodontics. Although it is recognized as being one of the most effective for both gutta-percha and sealers [18,19], its use has been questioned due to its cytotoxicity and carcinogenic potential [20–22]. Although, in general, the cytotoxicity of gutta-percha solvents depends on their exposure time and dose, chloroform also has a considerable storage risk, as it is highly flammable. In turn, halothane, also associated with a high level of toxicity, has been discontinued [23]. Other solvents such as xylene and eucalyptol, which have been proposed as being alternatives to chloroform, although quite effective [24,25], have been shown to address similar concerns, namely regarding biocompatibility [20,26,27]. TCE was reported as having a strong dissolution effect, particularly over gutta-percha [28]. Although it has been pointed out as also promoting the dissolution of endodontic sealers, it was clearly less effective than chloroform [12,29]. Essential oils, such as OOil, which have recently been stressed as “green compounds”, were considered as being quite safer but less effective, particularly for sealer dissolution [24,27,28].

3. Solvent Specificity

Targeting the chemistry of a resin epoxy-based sealer, MEK (also known as 2-butanone or methyl ethyl ketone) and ethyl acetate (also known as 1-acetoxyethane or acetic ester) have raised attention as being novel endodontic solvents [12]. MEK is an organic, colorless, water-soluble solvent with a sweet odor that is reminiscent of acetone, and is categorized in group D (not carcinogenic to humans) [30]. It has been especially highlighted for the dissolution of one of the most commonly used endodontic sealers: AH-Plus [12]. Based on the same principle of a targeted approach to a sealer′s chemistry, 10% formic acid and 17% ethylenediaminetetraacetic acid (EDTA) have recently been suggested for hydraulic sealer dissolution in the clinical retreatment protocol [31].

Although traditional solvents have been indistinctively used for both filling materials—gutta-percha and sealers (such as resin and zinc-eugenol-based)—there has always been a special focus on their gutta-percha dissolution profile. However, different compounds have emerged as quite specific sealer solvents, such as EndoSolv E (Septodont) (a tetrachloroethy lene-based compound) and EndoSolv R (Septodont) (a formamide and phenyl ethylic alcohol-based compound) for zinc oxide–eugenol-based and resin-based sealers. Recently, they have been replaced by EndoSolv (Septodont), the main constituents of which are ethyl acetate (50–100%) and pentyl acetate (2.5–10%) [32]. Even though its manufacturer claims that it can be used for different types of sealers, there are no sound reports regarding its efficacy.

The development of new rotary retreatment files may have contributed to a lesser focus on investigating solvents for NSER. However, microtomography, scanning electronic microscopy findings, and histobacteriological analysis have shown that, independently of the instrumentation system or the supplementary irrigating approach, filling residues and resistant biofilms still persist in root canals or dentinal tubules after NSER conventional procedures [2,15,16].

The use of traditional gutta-percha solvents is mostly isolated. However, a few studies have assessed some associations for better performance. Faria-Junior et al. [33] revealed that TCE potentiated the effect of OOil and eucalyptol in different types of gutta-percha and Resilon. The association between Citrol+TCE obtained the best results on Resilon′s dissolution, while OOil (citrol) alone obtained the worst; however, they were still quite milder. In the same sense, Citrol+TCE and Eucalyptol+TCE were the most successful among associated and isolated compounds against EndoREZ cones. The lack of a deeper explanation and concerns regarding their biocompatibility pointed out the need for further research. Recently, with the same methodology of weight loss percentage, Ferreira I et al. [12] presented MEK as having a higher efficacy for resin-based-sealer dissolution. The values obtained reached those of chloroform; thus, they were quite different to the traditional gutta-percha solvents studied. Additionally, the authors confirmed the efficacies of two binary mixtures with MEK as a common compound and organic/essential oil as a co-solvent: MEK/TCE and MEK/OOil. A synergistic effect explained their increased efficacy for gutta-percha and resin sealer dissolution. The mixtures' performances reached the gold standard of chloroform and, importantly, with a safer profile [13].

4. Moment of Use

Traditionally, solvents were applied at the initial stages of the NSER, when fillings are more compact, through the deposition of a few drops into the space created by the coronal filling removal [3]. The main objective was to soften gutta-percha, enabling the initial penetration of the file into the remaining obturation [5]. Some authors reported a negative impact of the solvents' deposition (chloroform and eucalyptol) in the medial and apical parts of the retreated ex-vivo canals, with reduced the filling remnants in the root canal surfaces of the nonsolvent groups [16]. Different methodologies, such as the type and moment of solvent deposition (before/after repreparation), may have influenced the results.

Flooding the canal with solvent after removing the bulk of the remaining gutta-percha, and further enlargement, have also been investigated. One of the studies assessed the effect of xylene (1 min) on cleaning the root canal with paper points; the outcome was comparable to 2.5% ultrasonically activated NaOCl [34]. In turn, Fruchi et al. [35] emphasized the cleaning performance of the reciprocating instruments with xylene (1 min) and concluded that, even with passive ultrasonic agitation (PUI), the solvent did not improve filling removal. Similarly, Barreto et al. [36] also showed no improvement with PUI with OOil or NaOCl. Contrarily, Ferreira I et al. [37,38] showed promising results, advising specific solvents (MEK/TCE and MEK/OOil) as an additional step after the conventional repreparation and NaOCl/EDTA treatment. Due to their high dissolution rate in short periods, the same solvent mixtures might also be considered, to assist with the initial penetration of well-compacted obturations.

5. Solvent Agitation

The goal of combining solvents with ultrasonic agitation (UA) was for endodontic instruments to reach difficult-to-access areas, enhancing their effectiveness, as with the current irrigating protocol [39]. Moreover, the apical root canal, which is considered a "critical zone" due to its strategic position for microorganisms, remains a challenge for several instrumentation techniques or irrigating/dressing proposals [40].

SEM assessments found no improvement in root canal walls cleanliness using PUI with EndoSolv R as a final step after further enlargement (repreparation), independent of the root canal thirds; thus, its efficacy remains unclear [41]. Additionally, with contradictory outcomes, a few ex-vivo studies with microtomography quantified the volume of the remnants of filling materials after retreatment protocols with solvent agitation. Barreto et al. [36] found no significant differences between static NaOCl, PUI/NaOCl, and PUI/OOil, but stressed that all groups showed a significant reduction in filling residuals (gutta-percha and epoxy resin-based sealer). The lack of superiority of the solvent group was justified with the formation of a paste that penetrated the dentinal tubules and canal irregularities, making its removal harder. Fruchi Lde et al. [35] concluded that solvent agitation (PUI for 1 min, with xylene) slightly increased filling material removal, but without statically significant results.

On the other hand, in vitro studies assessing the dissolution rate using a sample weight comparison concluded that UA increased the efficacy of solvents such as eucalyptol and OOil. However, independent of the solvent, the greatest dissolution was obtained with the ZOE sealer [42]. Another study [43] with chloroform and eucalyptol corroborated an increased efficiency of solvents in the dissolution of sealers with UA, although with a significant decrease concerning the mineral trioxide aggregate sealer (MTA Fillapex). Ferreira I et al. [12] also reported a positive impact of UA on solvent efficacy, which was first evidenced with MEK over an epoxy resin-based sealer (AH-Plus). Similarly, traditionally milder solvents, such as OOil, were clearly improved via UA with regard to gutta-percha dissolution [28].

Because MEK had little effect on gutta-percha dissolution, studies with the MEK/TCE and MEK/OOil associations have confirmed previous findings and a clear benefit of UA in filling dissolution [13]. The suggested protocol assessed in ex-vivo studies with microtomography, including MEK/TCE, and claimed to target the most common filling materials: gutta-percha and epoxy resin-based sealer (AH-Plus). These performances was reported as being similar to a further enlargement to the next file size, thus preventing an excessive reduction in the thickness of the root canals [38]. The authors also found that the benefit of solvent agitation was independent of the device, whether ultrasonic or XP-endo Finisher R [37]. The specificity and synergism of the solvents in the mixture, their moment of use, and the exposure time, as well as sonic/ultrasonic agitation, were given as explanations for the performance obtained.

6. Biocompatibility

NSER procedures are inevitably associated with more post-operative complications, due to a higher risk of extrusion. In addition to necrotic infected pulp residues and debris that can be pushed out of root canals, there is a risk of extrusion of filling materials and/or irrigating solutions and dressings. The biocompatibility of any compound used is, thus, a safety requirement. An ideal root canal irrigating solution should be biocompatible because of its close contact with the periodontal tissues, and should respect the biological and mechanical integrity of the tooth [44].

Although solvents have almost fallen into disuse with the advent of new retreatment instruments, a recent review emphasizes the heterogeneity of the studies published and encourages a pursuit of the comparison of compounds in different scenarios [45]. Despite the disparity of methodologies, most of the reported findings are based on the performances of traditional solvents, namely chloroform, eucalyptol, EndoSolv R, and xylol; with new and less cytotoxic proposals, such as orange essential oils, having insufficient dissolution properties to justify their use. Although the most effective solvents are generally recognized as being highly cytotoxic, using small amounts inside treated root canals may prevent concerns regarding the risk of extrusion [20,26,27,46,47]. Nevertheless, inadvertent contact with the periapical tissues could pose a risk to the patient.

The new strategy of combining solvents with agitation in the empty root canal after filling removal might raise additional concerns. One example is the suggested protocol with MEK/TCE or MEK/OOil, even though in-vitro studies have reported a lower cytotoxicity from these novel proposals compared to the isolated compounds or the gold standard, chloroform [13]. Moreover, the use of solvents as an adjunct to mechanical instrumentation has not been associated with higher extrusion [48,49] or poor post-operative conditions [50]. Nonetheless, prospective randomized studies are always needed to assess the clinical performances of new strategies.

7. Effects on Dentin Structure

During NSER, solvents are inevitably in contact with dentin for some time. For a long time, investigations have highlighted a decrease in enamel and dentin hardness, due to the significant softening effects of chloroform, xylene, and halothane, with a time-dependent effect [51]; however, others do not confirm these findings [52,53]. Recent protocols suggest longer periods of dentin exposure to solvents after removing the bulk of the obturations. Some apprehension has, thus, arisen as to whether solvents can alter the dentin surface's chemical composition, with potential changes in its microhardness, and consequences on the bond strength of the sealers [53,54]. A recent systematic review [55], including push-out assessments, has stressed that the heterogeneity of the studies prevented a reliable conclusion from being reached. However, chloroform and xylene seemed to raise further concerns.

Despite reducing dentin's hardness, the novel solvent proposals of MEK and ethyl acetate are reported as being preferred over chloroform, which caused the most significant decrease [56]. A different experimental design associating MEK with the specific co-solvents TCE and OOil significantly increased dentin hardness after NaOCl and EDTA treatment [57]. Regarding direct dentin exposure, the MEK/TCE group showed no significant differences from the control (saline). MEK/OOil produced a significant hardness increase, independently of being used directly or after the NaOCl/EDTA standard final irrigating protocol.

The effect of solvent agitation on dentinal structure, per se, has been scarcely studied, and with ambiguous results. UA was reported to elicit a decline in dentin hardness when using MEK, ethyl acetate, and chloroform [56]. On the other hand, a study with the solvent mixtures MEK/TCE and MEK/OOil found no evidence of UA causing an additional decrease in dentin's hardness [57]. Findings from endodontic irrigating solutions such as NaOCl, chlorhexidine, or EDTA also tend to diverge. Investigations on EDTA's effect on dentin microhardness found that diode laser agitation caused higher hardness reduction than EDTA alone. However, there were no significant differences with UA or photon-induced photoacoustic streaming [58,59]. The different methodologies and chemistries regarding the compounds might explain the contradictory outcomes.

8. Antimicrobial/Antibiofilm Activity

AP is currently recognized as a biofilm-induced disease [60]. This causal link explains the increased resistance of endodontic intra-radicular infections to conventional disinfection procedures associated with the number of unprepared areas where root canal microorganisms, in planktonic and especially biofilm form, may persist [11,60]. These are considered to be the main causes of treatment failure. Moreover, the awareness that bacterial biofilms occur with particular relevance in the apical portion is crucial for the treatment, indicating the importance of primary and post-treatment AP therapeutics [61].

Research focusing on the antimicrobial properties of conventional gutta-percha solvents, such as halothane, eucalyptol, and OOil, has not been deep. The reported assays are almost exclusively against planktonic bacteria, such as *Enterococcus faecalis* (*E. faecalis*) and *Staphylococcus aureus* (*S. aureus*). In general, findings agree upon a stronger degree of antibacterial activity that is associated with the most cytotoxic solvents; OOil, for example, shows no antibacterial activity against the species mentioned [62]. Ex vivo studies emphasize that chloroform reduces intracanal levels of cultivable *E. faecalis* during endodontic retreatment [63]. By also stressing the role of *E. faecalis* as being the prime etiological agent of post-treatment infection, Subbiya A et al. [64] highlighted that RC Solve, a derivative of OOil, had superior antibacterial activity compared to xylene and EndoSolv E, which has tetrachloroethylene as its major compound. That study considered the minimal inhibitory concentration against *E. faecalis* ATCC and a clinical isolate from a failed root canal.

Maximum antimicrobial activity against *E. faecalis* biofilm has been reported with the association of a surfactant, such as cetrimide, and with chloroform, eucalyptol, or OOil. Although the combinations with cetrimide achieved a 100% kill rate, cytotoxicity assessments or the dissolution efficacy of the suggested associations were missing [65]. Biofilm removal strategies include its disruption via chemo-mechanical preparation with specific shaping techniques, and antimicrobial irrigating solutions/dressings. Increased concern over its resistance to conventional antimicrobial drugs should be considered [66,67].

Supplementary procedures for activating the final irrigating protocol with NaOCl with recent devices, such as ultrasonics or XP-endo Finisher R, have been suggested [5,6]. However, microorganisms are reported to regrow after NaOCl treatment. Although the final exposure with the chelating EDTA had an additional antimicrobial effect, authors claim there is a flaw in its ability to completely eliminate resistant biofilms, such as *C. albicans*, the most prevalent fungi isolated from persistent endodontic infections [14,68]. A recent study highlighted that the association of MEK/OOil could eradicate *C. albicans* biofilm cells remaining after the conventional NaOCl and EDTA final irrigating protocol [14]. To our knowledge, this is one of the first reports regarding the antibiofilm activity of solvents over endodontic microorganisms, refractory to the NaOCl and EDTA protocol, while exhibiting excellent dissolution ability over the most common filling materials.

9. Future Directions

The causative agents of post-treatment disease have been exhaustively investigated, confirming a less diverse set of microbiota and lower cell counts in well-treated teeth. *Streptococcus* species and the usually reported *E. faecalis* are among the most common bacteria that are isolated in secondary infections [69]. *E. faecalis* has been especially implicated, probably due to its ability to survive in mono-infections under adverse conditions [69]. Nevertheless, nearly 55% of the microbial community belongs to uncultivated or uncharacterized phylotypes, which may be dominant in some cases, and the common association of *E. faecalis* with secondary infections is not definitively supported [70]. Moreover, *Fusobacterium* spp. and *Pseudomonas* spp. with *Streptococcus* and *Actinobacteria* spp. have recently been reported as the most dominant taxa. Regarding fungi, *C. albicans* is recognized as the most frequently identified [61].

In addition to the wider microbial knowledge regarding endodontic microbial diversity, new concepts are developing, such as the awareness of proteins, which are often associated with virulence and with resistance to antibiotics, and the dependency on the host's individual profile [61]. Rapid and accurate chair-side tests for quick microbial detection, together with the knowledge of antibiotic resistance genes, could eventually address a rapid microbiological diagnosis, enabling the best therapy. Meanwhile, advances in antibiofilm-effective adjunctive protocols might be important for reducing the bacterial load, improving the success rate of endodontic treatments.

10. Concluding Remarks and Limitations

One of the limitations of the present paper is the risk of bias in the strategy of the literature search. However, a systematic review was not the objective here, but rather, the identification of relevant directions for endodontic investigation, from the authors' point of view.

Research findings on new endodontic solvent proposals changed the paradigm by considering the use of solvents, not only for initial filling softening, but also in the final process as an adjunctive in removing filling residues and disrupting refractory biofilms. There is some evidence for the advantage of an additional step with specific and safe solvent proposals, such as the dual role of promoting the dissolution of filling materials, and an antibiofilm effect. These nonantibiotic agents may be a strategy for optimizing retreatment procedures in order for a better outcome of post-treatment disease.

Basic science is important for investigating singular hypotheses that can contribute to a deeper understanding of complex processes. However, prospective studies clarifying the roles of novel protocols in the outcome of the clinical (re)treatment of endodontic infections are missing. The development of novel strategies that understand and that reach endodontic microbial communities is crucial for achieving the necessary level of infection control that results in an improved long-term treatment outcome.

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