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Review Article

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Triple antibiotic paste: momentous roles and applications in endodontics: a review

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ABSTRACT

This study investigated the latest findings and notions regarding 'triple antibiotic paste' (TAP) and its applications in dentistry, particularly endodontics. TAP is a combination of 3 antibiotics, ciprofloxacin, metronidazole, and minocycline. Despite the problems and pitfalls research pertaining to this paste has unveiled, it has been vastly used in endodontic treatments. The paste's applications vary, from vital pulp therapy to the recently introduced regeneration and revascularisation protocol. Studies have shown that the paste can eliminate the root canal microorganisms and prepare an appropriate matrix for further treatments. This combination is able to remove diverse groups of obligate and facultative gram-positive and gram-negative bacteria, providing an environment for healing. In regeneration protocol cases, this allows the development, disinfection, and possible sterilization of the root canal system, so that new tissue can infiltrate and grow into the radicular area. Moreover, TAP is capable of creating a discipline in which other wanted and needed treatments can be successfully performed. In conclusion, TAP, as an antibacterial intracanal medication, has diverse uses. Nevertheless, despite its positive effects, the paste has shown drawbacks. Further research concerning the combined paste and other intracanal medications to control microbiota is a must.

Keywords: Antibiotic; Apexification; Endodontic treatment; Pulp regeneration; Triple antibiotic paste

INTRODUCTION

Endodontic treatments are one of the most important and premiere therapies in the world of dentistry; they permit proper tooth function and maintain the dental structure in the oral cavity [1]. Different methods and strategies have been advocated, from the traditional step-back preparation technique to new contemporary approaches, all of which have shown various degrees of success and failure in teeth with a variety of pulp-periapical conditions [2]. Gradually, and as an adjunct to clinical approaches, root canal medicaments, particularly antibiotics, started to reveal their indispensable significance and pivotal rule in achieving successful outcomes [3].

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Antibiotic therapy has become an inseparable part of diverse medical and medical-related treatments, and acts as the one of the main fronts against microorganisms [4]. Various antibiotics with divergent formulas are used, for prevention and prophylaxis, to cure active and acute infections and diseases [5,6]. There are different routes in classifying antibiotics; for example, these drugs can be divided into several subclasses; cillins, mycins and porines are instances of such divisions. In other schools of thought, they are categorized according to the types of bacteria they are effective against; like antibiotics that affect gram positive and gram-negative microorganisms or the ones which target strict and facultative aerobes and anaerobes [7,8]. Also, different sets of drugs, like penicillin and its derivatives, consist of diverse formula which represents their characteristics, features, and properties; e.g., amoxicillin differs from ampicillin and penicillin V, both in the range of bacteria it affects and in the way the drug is prescribed. Also, clindamycin, in spite of belonging to the same class of antibiotics, is different from erythromycin as far as microorganisms are concerned [8]. Cillins generally strike gram-positive bacteria whilst an antibiotic like metronidazole is useful for combating gram-negative ones [9]. Thus, in many cases when groups of numerous bacteria are involved, a combination of antibiotics is used; dentistry is not an exception to this rule [10].

Odontogenic infections originate from the dental structure, and like any other infections in our body they engage a huge number of different microbes and microorganisms [2]. Therefore, to confront an odontogenic derived infection, combinations of drugs particularly antibiotics are needed to combat the microbiota responsible for creating the lesion. That is why many antibiotics have been investigated, studied, and used to control and defeat dental infections [11]. The very first use of an antibiotic in endodontics dates back to 1951, when Grossman used a poly-antibiotic formula known as PBSC, a paste in a silicone vehicle and a combination of penicillin, bacitracin, streptomycin, and caprylate sodium [12]. PBSC contained penicillin to affect gram-positive organisms, bacitracin to target penicillin-resistant strains, streptomycin for gram-negative organisms, and sodium caprylate for yeasts. The clinical assessment of PBSC showed therapeutic effects; nevertheless, the formula was not very effective against anaerobic microorganisms that play a pivotal role in endodontic diseases. As a consequence, and in addition to the risk of sensitization and allergy to penicillin, the USA Food and Drug Administration banned PBSC for endodontic use in 1975 [13]. In 2006, the American Association of Endodontists introduced an article regarding several antibiotics for endodontic infections to control root canal microbiota which appear to have a key role in the pathogenesis and progression of the pulp and periapical pathosis [14].

REVIEW

The very first aim of endodontic treatments is to eliminate as many bacteria as possible from the root canal system and create an environment in which no remaining microorganisms can survive [15]. Ideally, this can only be obtained through the use of a combination of aseptic treatment techniques, chemo-mechanical preparation of the root canal, antimicrobial irrigation, and intracanal medicaments [15,16]. Approximately 50 percent of root canal peripherals and ramifications may remain uninstrumented during preparation of the root canal [17]. In this condition, the remaining necrotic tissues may act as a nutrition source for the surviving bacteria [18,19]. Thorough and systemic mechanical instrumentation,

irrigation, and use of inter-appointment medication can perhaps reduce this phenomenon. Medicaments can play an important role in the preparation of the root canal for further therapies [17], for example in necrotic pulps and active exudation [20]. Calcium hydroxide has long been used as an inseparable part of root canal treatment in necrotic cases, resulting in less signs and symptoms. Traditionally, calcium hydroxide has been used in open-apex teeth with necrotic pulp tissues for inducing a bridge and preparing the root canal space for forthcoming therapies. Without the use of inter-appointment intracanal medications, such successful results are far-fetched [20,21].

The type of intracanal medication depends upon the precise diagnosis of the tooth condition, a thorough knowledge of the type of microorganisms involved, and finally, their mechanisms of growth and survival. The presence of bacteria within the root canal is the main factor of endodontic disease, and therefore the use of an antimicrobial agent is essential. Many forms of intracanal medicaments, apart from antibiotics and calcium hydroxide have been used in an attempt to accomplish the above aim [22]. These mainly include chlorhexidine and ethylenediaminetetraacetic acid [23].

Currently, the common antibiotic-containing commercial pastes are Ledermix (Lederle Pharmaceuticals, Wolfratshausen, Germany) and Septomixine Forte (Septodont, Saint-Maur, France) [24,25]. Both preparations have corticosteroids as anti-inflammatory agents. However, neither of these pastes can be considered suitable for use against endodontic microbiota owing to their inappropriate spectrum of activity [17,23]. Several studies have investigated different root canal antibiotic agents [26].

Recently, another combination of antibiotics, called 'triple antibiotic paste' (TAP) was introduced especially for the regeneration and revascularization protocol and the treatment of open apex teeth with necrotic pulp. This material has also shown other applications in endodontics [25]. Initially, TAP was largely developed by Hoshino and colleagues [24], who investigated the effectiveness of the paste on the removal of microorganisms from the root canals [27]. Researchers have also used TAP *in vitro* to disinfect *Escherichia coli*-infected dentine [27]. Later, particular attention was given to the antibiotic paste and its effect against microorganisms present in carious dentine and infected pulp. The outcome showed excellent results in the eradication of the bacteria from the radicular system [28].

TAP is a combination of ciprofloxacin, metronidazole and minocycline [29]. Metronidazole, as a nitroimidazole compound, is particularly toxic to anaerobes and is considered an antimicrobial agent against protozoa and anaerobic bacteria. Minocycline is bacteriostatic and shows activity against gram-positive and gram-negative bacteria. It also causes an increase in the amount of interleukin-10, which is an inflammatory cytokine. Moreover, ciprofloxacin — as a synthetic fluoroquinolone — possesses fast bactericidal action and exhibits high antimicrobial activity against gram-negative bacteria, whilst limited activity against gram-positive ones. Many anaerobic bacteria are resistant to ciprofloxacin. Hence, it is often used with metronidazole in treating mixed infections to compensate for its limited scope [30]. Therefore, TAP can affect gram-negative, gram-positive, and anaerobic bacteria, and this combination can be effective against odontogenic microorganisms [31].

If the TAP is to be used, ciprofloxacin, metronidazole, and minocycline should be mixed equally (1:1:1) [2,25,32] to a final concentration of 0.1–1.0 mg/mL [33,34].

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Applications of TAP in endodontics

The applications of TAP in endodontics can be considered as follows:

1. In the regeneration and revascularization protocol of the pulp
2. As an intracanal medicament for the treatment of
   1) Periapical lesions
   2) External inflammatory root resorption
   3) Root fracture
   4) Primary teeth
3. As an intracanal agent to control flare-ups
4. As a medicated sealer (to prevent possible re-infection)
5. As an additive to gutta-percha points in root canal obturation (known as medicated gutta-percha points)
6. As an intracanal medicament loaded on a scaffold

1. In the regeneration and revascularization protocol of the pulp

Recently, Regenerative Medicine, especially at the molecular and cellular level, has been given great attention. Clinically, medical professionals are inclining towards 'regeneration' instead of 'replacement' approaches [35]; resulting in state-of-the-art definitions such as 'vital pulp therapy' and 'regenerative endodontics' [35,36]. In such treatments, clean environment is believed to be a necessity for further success. TAP, which was originally introduced by Banchs and Trope [25], is widely used to achieve a relatively aseptic environment in the radicular space so that the tissue repair and healing can occur [37]. Promising results have attracted numerous endodontists and enthusiastic general dental practitioners to endodontic regenerative procedures (ERPs) [38] which is considered as a form of a revolution in root canal therapy [38-41]. ERP has now been taken into account as an alternative method to calcium hydroxide-induced apexification, in which the TAP is used as a dressing material instead of the traditional calcium hydroxide [42-45]. Pulp revascularization, the second component of the regeneration protocol, is desired in the treatment of immature permanent teeth with necrotic pulp and apical periodontitis [44]. And it has managed to exhibit thickening of radicular walls, closure of apical foramen [45], continued root development, and recovery of a relatively positive response to electric pulp testing [37,46]. Clinically, to regenerate and vascularize the pulp, an over-instrumentation is carried out to provide bleeding and consequently stimulation of stem cells into the radicular space. The placement of intracanal medicaments are necessary for this process [47,48].

TAP should be used in the safest possible concentration (1 mg/mL) [44] since higher dosages could have undesired results on the stem cells [49]. Even at low concentrations, TAP has unwanted effects on the proliferative capacity and mineralized matrix formation of dental pulp cells and apical papilla cells [50]. According to several studies, a concentration of 0.125 mg/mL of TAP has no cytotoxic effect on the stem cells; thus, it is expected that a concentration of the antibiotic combination with the lowest possible side effects and adequate ability for removing microorganisms, particularly *Enterococcus faecalis* (*E. faecalis*) must be used during endodontic treatments [50,51]. The proper and careful combination of the 3 antibiotics has shown to create an appropriate environment for the cell attachment to occur, and to have enough dislocation resistance [52] for mineral trioxide aggregate (MTA) or calcium enriched mixture (CEM) cement as the bio-regenerative dressing.

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Since ERP has presented itself as a promising alternative for the treatment of immature teeth with necrotic pulps, it has been compared with other methods and strategies of such therapies (MTA apical plug), to evaluate the closure of open apices [53]. It was revealed that both treatments succeeded in the closing of the foramen. However, in cases of TAP, an increase in root length in combination with thickening of dentinal walls were also observed [44,54]. Another research has indicated that root maturation after regenerative endodontics is different case by case; depending upon various factors such as time and duration of the treatment, angulations of intra-oral film, method of radiography, anatomic landmarks, and so forth [55]. TAP has also shown a significant antibacterial effect in the radicular dentine compared with the untreated dentine, which helps to disinfect and eradicate endodontic pathogens; a pivotal factor in regeneration and revascularization procedures [56].

Recently, an innovative approach based on the regeneration and revascularization protocol, named 'SealBio,' has been introduced to deal with pulp and periapical problems [57,58]. SealBio is claimed to be a simple, non-obturation, easy-to-do, and cost-effective technique with excellent outcomes [59]. Similar to the ERP, thorough disinfection and optimal removal of the bacteria in the root canal system is necessary for success. TAP [60] and modified triple antibiotic paste (MTAP), a combination of metrogyl (metronidazole), ciprofloxacin, and tetracycline [57], have been considered as they are effective on the deeper layers of dentine [60] in the SealBio treatment regime.

Tooth discoloration is said to be a repercussion of minocycline as a component of the intracanal medicament [61,62] and cited as a drawback of the paste. Despite the removal of minocycline from the antibiotic combination and replacement with Cefaclor (a member of the second generation cephalosporins), the defacement of clindamycin and amoxicillin will appear sometimes immediately after treatment and in some cases after a delay [20,37,62]. In several papers, discoloration is blamed on MTA [63]; although further research is needed for better understanding of the cause of such discrepancy [64]. Reynolds *et al.* [65] believed that if dentinal tubules in the pulp chamber are coated with a bonding agent, discoloration can be minimized.

In vitro observations have also indicated that in cases where TAP is used in regenerative endodontics, higher dentine demineralization and a reduction in dentine micro-hardness due to changes in the chemical structure of the superficial dentine can be seen when compared with calcium hydroxide [66,67].

Another negative side effect to the conditioning of the radicular dentine by TAP seems to be the indirect adverse effect on the stem cells of apical papilla (SCAP) and their survival. It has been shown that dentine conditioning with TAP at commonly used clinical concentration (approximately 1,000 mg/mL) prevents SCAP from survival, but if the concentration is altered and modified to 1 mg/mL, this detrimental effect can be avoided. Lower concentrations (0.1 and 0.01 mg/mL) have also shown no detectable effect on SCAP and therefore it seems that a concentration higher than 1 mg/mL can be lethal to the said stem cells [68]. This contrasts the use of dentine conditioning by calcium hydroxide which promotes SCAP survival and proliferation [49].

2. As an intracanal medicament

TAP is said to serve as an antiseptic agent which can be applied onto the walls of the radicular system to remove microorganisms before or after cleaning, shaping, and irrigating the root

canal area [17]. Such an action will result in the reduction or elimination of microorganisms, prevention of post-treatment pain, and enhancement of anesthesia [41]. In a study, Murvindran and James [17] demonstrated the ability of TAP in removing microbiota and preparing a suitable environment for further endodontic treatments, whilst Kim and Kim [69] reported that TAP showed a larger inhibition zones against *E. faecalis* than calcium hydroxide.

1) For the treatment of periapical lesions

Periradicular lesions associated with non-vital teeth can be generally grouped as periapical abscess, granuloma or cyst. Zain *et al.* [70] reported that the presence of a large size periapical radiolucency is more likely to be a peri-radicular cyst. Various treatment approaches to manage a large periapical lesion can be classified as either surgical or non-surgical endodontic therapies [71]. Since surgical endodontics has its own problems, it is advisable to initially treat periradicular lesions in a conservative manner by a non-surgical endodontic therapy, usually with the use of an antimicrobial intracanal medicament [71,72]. Özan and Er [73] found that the combination of antibiotic drugs in TAP as an antibacterial dressing, is successful in healing large cyst-like lesions. TAP in other endodontic treatments is considered prior to any sort of surgery. It has been suggested that the TAP can be considered and used with intracanal aspiration in order to successfully cope with a large periapical and cyst-like lesion [74]. TAP has also been used for the treatment of cystic lesions as a multidisciplinary approach including root canal therapy and endodontic surgery [30]. Apparently, other most commonly used medicaments have not succeeded eliminating the signs and symptoms, and disease from its location [75].

2) For the treatment of external inflammatory root resorption

Several studies have shown the importance of TAP in the treatment of external inflammatory root resorption (EIRR). Treatment of such clinical challenges often require the regeneration and revascularization protocol; which in itself consists of disinfecting the root canal system with TAP [24], filling the radicular area with blood clot, and sealing the root canal(s) with MTA and bonded resin restoration [25]. TAP is the most common medication recently used in EIRR although some other medications were also prescribed [76]. It has been shown that this combination of drugs is able to enter dentinal tubules [77] and can kill any bacteria in the carious lesions, necrotic pulp, infected root dentine, and peri-apical lesions [77,78], and thus, stop the resorption process [79].

3) For the treatment of root fracture

Several clinical studies and case reports on teeth with horizontal root fracture and their corresponding treatment with TAP as the intracanal medicament, and MTA as the coronal obturator have radiographically demonstrated repair of the fractured root with the disappearance of the tooth symptoms after a period of 12 months [80]. It is believed that such nonsurgical endodontic management owes its success to the disinfection and the microorganism removal by the TAP resulting satisfactory healing between the broken fragments [24,80,81].

4) For the treatment of primary teeth

Previous research in pediatric dentistry has illustrated that TAP can be used in a very effective way with good clinical success in primary teeth [82]. However, intracanal medication should not replace the instrumentation phase since the antibiotic agents alone cannot eradicate canal infection in long term [64]. In these studies, non-instrumentation endodontic treatment 'Lesion Sterilization and Tissue Repair' and the triple antibiotic the paste were used [82,83].

3. As an intracanal agent to control flare-ups

Several studies have shown the effect of TAP in controlling endodontic flare-ups [84] in diabetic patients between treatment appointments. Interestingly, TAP has shown to be more effective than calcium hydroxide in these patients [85]. The combination of the 3 existing antibiotics seems to be able to defeat bacterial resistance and subsequently result in increased antimicrobial action [86]. The anti-inflammatory ability of minocycline can synergistically assist in treating the disease [87,88].

4. As a medicated sealer (to prevent possible re-infection)

TAP has been claimed to be effective against *E. faecalis*, the microorganism which is said to be the most dominant in persistent endodontic infections [89]. TAP has been added to zinc oxide eugenol-based root canal sealers in order to prevent re-infection and to provide extended antimicrobial property to the sealer [90]. Hoelscher *et al.* [91] found that amoxicillin, penicillin, clindamycin, and doxycycline relatively enriched the antimicrobial efficacy of Pulp Canal Sealer EWT (Kerr Corporation, Romulus, MI, USA) against *E. faecalis*. It has been shown that if amoxicillin, doxycycline, and metronidazole are added to Kerr Pulp Canal Sealer, the antibacterial property and apical sealing ability of the material can improve in addition to the increased working time [91,92]. Sharma *et al.* [93] showed that AH26 (Dentsply, Tulsa Dental, Tulsa, OK, USA) with amoxicillin and doxycycline is effective in removing *E. faecalis* from dentinal tubules [91,93,94]. Kangarlou *et al.* [95] showed that TAP improves the antibacterial properties of AH26 and AH plus endodontic sealers. However, Bansal and Jain [13] argued that though TAP can be combined with some root canal sealers, the mixture of TAP with sealers is currently not recommended and that further investigations are needed.

5. As an additive to gutta-percha points in root canal obturation (known as medicated gutta-percha points)

If root canal obturation material includes antibacterials, it can help eliminate microorganisms which are left behind in the anatomical complexities of the radicular area; such as secondary canals, dentinal tubules and isthmus, or areas that biomechanical preparation of root canal system is missed [96]. Gutta-percha points which include metronidazole for disinfecting the root canal system have been studied, and might be regarded an effective ingredient to the obturation material [97]. Indeed, such application needs further *in vivo* studies to investigate the toxicity, antibacterial, and antifungal effects [97,98] as well as long term effects on antibacterial resistance in individuals especially with dangerous diseases such as tuberculosis.

6. As an intracanal medicament loaded on a scaffold

A growing body of evidence has shown the importance of TAP on a scaffold system, due to the potential to remove and eradicate microorganisms and their biofilm (e.g., *Actinomyces naeslundii*); a crucial step in endodontic regeneration [99].

Using low concentration of antibiotics on a scaffold in the radicular area has recently attracted attention. TAP, in an effective concentration has no significant sign of being cytotoxic to the stem cells and has demonstrated an ability to stay in the area without further dilution [50]. Also, bioresorbable antibiotic-loaded scaffolds and fibers have been further investigated in endodontic regeneration protocol [100]. In one particular study, an incorporation between double antibiotic paste (DAP) and a nano-fibrous scaffold showed promising potential as a drug delivery system [101].

Special consideration

1. TAP and radicular dentine

A number of studies have revealed that the TAP and the concentration used for regeneration and revascularization protocol may cause significant loss of dentine and a substantial increase in its roughness [102,103]. Such an increase can result in lower dentine wettability, and an enormous amount of reduction in the inorganic phase of the treated dentine in addition to the considerable increase in the organic phase. TAP with its acidic capability (pH = 2.9) [100] can demineralize the dentine surface [104]. Also, research and attenuated total reflection-fourier transform infrared spectroscopy measurements indicated that 1 g/mL TAP showed severe reduction in micro-hardness of the root and demineralization of the dentine. However, if 1 mg/mL methylcellulose-based TAP is used (in comparison with 1 g/mL TAP), this detrimental effect can be reduced. Other literature has suggested that using lower concentrations will again minimize this problem and therefore optimize radicular canal erosion and surface roughness [67,105]. TAP seems to be responsible for adversely affecting the fracture resistance of root canal dentine, particularly when the TAP is compared with chlorhexidine as an intracanal medicament [106].

Several research cases have also demonstrated a greater increase in the root length in teeth treated with TAP when compared with MTA, calcium hydroxide, and formocresol [102]. It seems that the TAP is capable of preparing a matrix for thickening the dentinal walls of the root [42] in comparison with calcium hydroxide and formocresol [107]; an effect which could play a significant role in shaping of the root canal [2,31].

2. Discoloration of the tooth structure

Teeth treated by the TAP have shown a degree of crown discoloration [20,37,108,109], likely that related to the existence of minocycline in the paste. In view of this, great care and caution should be taken in aesthetic zones [25,37,72,107,110]. A number of medicinal replacements, such as amoxicillin [111], Arestin (OraPharma, Inc., Warminster, PA, USA) [112], and Cefaclor (a member of the second generation cephalosporins) have been used to prevent the problem [37,113-115]. Recently, the Minocycline-removed paste or DAP have found its place [33,72]. 'European Society of Endodontology' advocates the use of calcium hydroxide so as to avoid discoloration [116].

In addition to such modifications in the formula of the paste, several strategies to make up for the discoloration have been investigated. The most commonly recommended is internal bleaching to remove cervical discoloration from the TAP [117]. Another approach is the application of dentine bonding agents or the use of composite resins as dentinal walls sealants [36]. Nonetheless, further evaluation and assessment of the results is necessary [55,108].

3. Removal of the paste

Another pitfall to consider during application of TAP in root canal space is the challenging removal of the paste. Existing irrigation techniques are not able to effectively remove TAP since it penetrates and binds into the dentinal structure [118,119]. Ultrasonic activation of 5.25% sodium hypochlorite seems to be the most effective method in removing the paste [61,120], contrary to chlorhexidine which seems to be the least effective intracanal irrigation solutions [121]. However, Arslan *et al.* [119] showed that 'photon-induced photo-acoustic streaming' (PIPS), which is a contemporary technique for removing materials from root canal walls, was more effective than needle irrigation in the removal of TAP from root canal system [119]. In a similar study, it was found that irrigation activation regiments of ultrasonic irrigation extremely

improved the removal of modified TAP from the root canals compared with conventional syringe irrigation [122]. In a recent investigation, Turkaydin *et al.* [123] used an XP-Endo Finisher to show that it can even remove more TAP than ultrasonic and syringe irrigation methods.

Moreover, the time and number of sessions needed to apply TAP, and the necessity of the removal are the other disadvantages in comparison with one-visit MTA apical barrier technique [36].

4. TAP and operative dentistry

The use of TAP as an antibiotic paste is not limited to endodontics. Investigations have revealed that glass ionomer cement (GIC) containing TAP is quite effective on *Streptococcus mutans* and *Lactobacillus casei*. Yesilyurt *et al.* [124] demonstrated that if the concentration of 1.5% TAP is added to GIC, the physical and bonding properties, the compressive strength, and the bonding strength to dentine are not modified and stay optimal.

CONCLUSIONS

If endodontics is to succeed, root canal microbiota should be properly reduced. Endodontic treatments rely mainly upon the elimination and possible eradication of the involved microbiota and their various virulent features from the root canal system. Biomechanical instrumentation, though an essential step, does not always provide such an environment in the root canal system. Non-instrumentation methods such as tooth repair and strategies towards maintaining a situation for regeneration and revascularization of the pulp should be considered, in which local use of drugs, particularly antibiotics, has shown their significance.

Amongst the combination of antibiotics, TAP, owing to its effectiveness on different microorganisms and its diverse applications and triumphs, is of particular interest in endodontics. However, development of resistant bacterial strains and tooth discoloration are some of its pitfalls. Nonetheless, TAP seems to be a successful combination of drugs in root canal disinfection/sterilization and pulp regeneration and revascularization protocol. All currently available antimicrobial materials for radicular irrigation and medication have their own benefits and limitations; the search for creating the ideal irrigant and inter-appointment medicament continues.

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