Topical Application of Antibiotics in Primary Teeth: An Overview

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ABSTRACT

Root canal infections are polymicrobial in nature, consisting of both aerobic and anaerobic species. The successful treatment of both primary and secondary endodontic infections involves effective eradication of the causative microorganisms during root canal treatment procedures. Reduction and elimination of microorganisms from the infected root canal provides optimal opportunity for treatment success. Local application of antibiotics has been considered an effective way to deliver antibiotics. A combination of antibiotic drugs have been tried under the concept of lesion sterilization and tissue repair therapy to eliminate the target bacteria, which are possible sources of endodontic lesions. The purpose of this article is to discuss the lesion sterilization and tissue repair therapy technique in primary teeth.

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Root canal infections are polymicrobial in nature, consisting of both aerobic and anaerobic species.[1] Recently, molecular approaches have confirmed the existence of mixed infections with predominant anaerobic bacteria, in permanent as well as infected primary teeth.[2,3] There is a diverse microbial profile with over 700 bacterial species and strains, over half of which were uncultivated bacteria (ie, new endodontic pathogens) detected in the oral cavity alone.[4]

Endodontic treatment of primary teeth with necrotic pulps is routinely done in dental practices. The successful treatment of both primary and secondary endodontic infections involves effective eradication of causative microorganisms during the root canal treatment procedures. This often presents a challenging task to the clinician, due to the typical primary tooth morphology (tortuous root canals, presence of multiple accessory canals, ramifications, and ample medullary bone spaces that favor dissemination of infection). In addition to that, obtaining a hermetic seal is difficult due to the lack of apical closure following physiologic root resorption owing to the close proximity of the developing permanent tooth germ to the roots of the primary teeth.[5-7] A further challenge presented to the dentist in rendering effective endodontic treatment is the behavior management of uncooperative children.

Numerous measures have been described to reduce the number of microorganisms using instrumentation techniques, irrigation regimens, and intracanal medicaments. The complexity of root canals, however, precludes complete elimination of bacteria from the root canal system by instrumentation alone. Hence, disinfection is deemed necessary to kill these microorganisms[8].

Use of topical antibiotics in endodontics dates back to the 1950s.[6,9] Early investigators tried a combination of antibacterial drugs like Grossman's polyantibiotic paste containing penicillin, bacitracin, or chloramphenicol and streptomycin.[10] Despite its therapeutic effect,

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it was ineffective against anaerobic species. Later, a mixture of neomycin, polymyxin, and nystatin[11] was tried, but the spectra of activity were unsuitable against the commonly reported endodontic bacteria.[9] Consequently, both these preparations had limited efficacy as intracanal medicaments. Recently, a combination of ciprofloxacin, metronidazole, and minocycline has been investigated in an effort to eliminate all bacteria from infected root canals.[12-14]

Local application of antibiotics is considered more effective than systemic administration. Because of the diverse microflora, and complexity of root canal infections, the use of a single antibiotic might not result in effective disinfection of the root canal system. To address this diverse microflora, a combination of antibiotic drugs was tested using lesion sterilization and tissue repair (**LSTR**)[8] by a group of Japanese researchers. The theory behind it is that the repair of damaged tissues might occur if lesions are disinfected. This technique has also been referred to as non-instrumentation endodontic treatment.[12,15,16] The purpose of this article is to discuss the LSTR technique in primary teeth.

INDICATIONS AND CONTRAINDICATIONS OF LSTR

LSTR is commonly indicated in infected teeth with an abscess/sinus tract, in cases of pathologic root resorption and/or spontaneous pain. The therapy is also indicated if there is a radiolucency in the bifurcation area and/or loss of alveolar bone radiographically. It is contraindicated in teeth with a perforated pulpal floor, radiographic evidence of excessive internal resorption, excessive bone loss in the furcation area involving underlying tooth germ, and in nonrestorable teeth.[7,12,13,17]

SELECTION OF DRUGS

The LSTR technique involves the use of 3 broad-spectrum antibiotics—ciprofloxacin, metronidazole, and minocycline (**3Mix**)—in a carrier of macrogol and propylene glycol (**MP**). This mixture is also known as triple antibiotic paste/polyantibiotic paste, antibiotic mixture, or mixed drugs. Metronidazole was selected as an appropriate drug given its activity against obligate anaerobes, which comprise the majority of bacteria in the root canal system.[18] It has been reported that it can penetrate into deeper layers of carious dentin and disinfect the lesions in vivo.[19] Metronidazole alone, however, even at a concentration of 100 µg/ml, cannot eradicate all of the bacteria,[15,20] indicating the need to add other drugs to sterilize infected root dentin.[13] Ciprofloxacin, a bactericidal agent effective against gram-negative species and minocycline, a long-acting bacteriostatic agent effective against a wide range of microorganisms, were added to metronidazole. These antibacterial drugs were selected based on the studies done to understand the target bacteria in LSTR endodontic treatment.[12,21-24]

PROTOCOL FOR PREPARATION OF 3MIX

If these drugs are enteric coated, the coating can be removed with a scalpel and pulverized using a mortar and pestle. Capsules can be separated and the powder should be stored in tightly capped containers.[16]

According to Takushige et al.,[12] 3Mix can be prepared in 2 ways: 3 Mix sealer (ie, 3Mix with canal sealer) or 3Mix with MP. The authors recommended 1 part of ciprofloxacin added to 3 parts minocycline and 3 parts of metronidazole. For the standard preparation, 1 part of MP should be mixed with 7 parts of 3Mix to get a blend that smears easily but does not crumble. To obtain a creamy consistency, a ratio of 1:5 (MP:3Mix) is recommended.[25]

TECHNIQUE

With the LSTR technique, local anesthesia and rubber dam isolation are recommended. Access to the pulp chamber is gained, the roof of the pulp chamber is removed, and either a pulpotomy[12] or a pulpectomy[13] can be completed.

Studies have recommended irrigating canals with saline[13,26] and treating dentinal walls with ethylene diamine tetra acetic acid (**EDTA**).[26,27] Hemorrhage is controlled by applying sterile cotton pellets moistened with sodium hypochlorite (**NaOCL**) against the pulp stumps for 1 minute.[17] The root canal orifices are enlarged to create a medication cavity (1 mm diameter and 2 mm depth) as a receptacle for the medicament.[12] The medication cavity is half-filled with a creamy 3Mix MP, or it can be placed over the pulpal floor if a medication cavity cannot be prepared. Following placement of the medicament, the orifice is sealed with glass ionomer cement (**GIC**)[7,12,13,17,27,28]and further reinforced by composite resin (**CR**)[12,13,27,28] and/or a stainless steel crown (**SSC**).[7,17,28]

METHOD FOR REVIEWING LSTR STUDIES

Comprehensive searches of the MEDLINE database were performed between 2008 and 2011. First-stage screening through PubMed identified all relevant studies, irrespective of the language of publication. The keywords used in the search related to primary teeth were: pulp therapy, 3Mix, metronidazole, ciprofloxacin, minocycline, endodontic treatment, lesion sterilization and tissue repair therapy, antibacterial drugs, noninstrumentation endodontic treatment, topical antibiotics in endodontics, bacterial profile, endodontic infection, and triple antibiotic paste. Two independent authors read the titles and abstracts of the 376 articles to determine their eligibility for inclusion. Clinical trials were selected with children of any age treated with LSTR in primary teeth displaying clinical, radiographic, and overall outcomes.

During the second-stage screening, articles were included from a hand search of the journals, references listed from primary sources, related citations, textbooks,

IndexCopernicus and web searches through specific journal websites not indexed. A total of 44 articles were selected for review, from which eventually 5 in vitro studies and 7 clinical articles were identified as potentially relevant. Articles in the English language were included, while studies that included permanent teeth, unpublished conference proceedings, and articles in Japanese with only English abstracts available were excluded. Full content of the selected articles was retrieved. These 44 articles were published between 1966 and 2011, while clinical trials were published from 2004 to 2011. Clinical trials had 55 citations in PubMed central, and 2 references were from the Textbook of Endodontics.[24,29]

LITERATURE REVIEW

IN VITRO TRIALS: EFFECTIVENESS OF MIXED ANTIBIOTICS

Sato et al.[21] evaluated the antibacterial efficacy of a mixture of ciprofloxacin, metronidazole, and minocycline with rifampicin (4Mix) and without (100 µg each/ml) against oral bacteria in children. Although more than 10^1 colony forming units (bacteria) occurred in samples taken from carious lesions, endodontic lesions, and periodontal pockets, none were recovered in vitro in the presence of either mixture, indicating that the mixed drugs inhibited growth of all the bacteria present in these samples. Additionally, in situ experiments confirmed the sterilization of dentinal lesions with 4Mix. They concluded that carious and endodontic lesions of primary teeth could be sterilized by topical application of the mixed drugs.

Sato et al.[22] evaluated the antibacterial efficacy of mixed antibacterial drugs on the bacteria of carious and endodontic lesions of human primary teeth in vitro. Minocycline is known to cause pigmentation, especially in calcifying teeth, so different combinations were tried: mixtures of ciprofloxacin, metronidazole, and a third antibiotic (amoxicillin, cefaclor, cefroxadine, fosfomycin, or rokitamycin). No bacteria were recovered in the presence of any combination of the mixtures (100 µg each/ml), but bacterial growth occurred on control plates (10^1 to 10^7 colony forming units). These findings indicated that mixed drugs could sterilize carious and endodontic lesions.

Hoshino et al.[23] investigated the antibacterial effect of 3Mix with rifam-picin (4Mix) and without on bacteria taken from the dentin of infected root canals. When combined, these drugs were able to consistently disinfect all samples at concentrations of 25 µg each/ml. Althoughrifampicin alone, at concentrations of 10 µg /ml, 25 µg /ml, 50 µg /ml, and 75µg /ml, substantially decreased the bacterial recovery, it could not kill all the bacteria. Additionally, rifampicin was not clinically acceptable due to discoloration.

Sato et al.[30] evaluated the potential of 3Mix to kill bacteria in the deeper layers of root canal dentin in situ. Twenty-four hours after applying it, no bacteria were recovered from the infected dentin of the root canal walls, except in one case in which a few bacteria were recovered. They concluded that this drug combination could penetrate into dentinal tubules and was effective against bacteria infecting the root canal dentinal walls.

EFFECTIVENESS AGAINST SECONDARY INFECTION

Enterococcus faecalis has recently gained attention in endodontics, as it can be frequently isolated from root canals, that failed treatment, sometimes even after treatment using calcium hydroxide. Hence, Alam et al.[31] evaluated the susceptibility of *E. faecalis* to the 3Mix drug mixture in vitro. The minimum inhibitory concentrations of ciprofloxacin and minocycline on *E. faecalis* and *Enterococcus faecium* were 5µg/ml to 20µg/ml, respectively, and no inhibitory effect was observed with metronidazole. 3Mix, at 100µg of each drug/ml, however, completely inhibited the growth of every strain.

CLINICAL TRIALS (TABLE 1)

Takushige et al.[12] evaluated the efficacy of 3Mix in ointment (ie, with MP) and of a root canal sealer on the clinical outcome of LSTR therapy in 56 4- to 18-year-old patients. Out of 87 primary teeth, 81 had physiologic root resorption and 54 radiolucent periradicular lesions were present. After accessing and extirpating the coronal necrotic pulp, the medicament was placed in the medication cavity, the access was sealed with GIC and a composite resin inlay was performed. They reported that the clinical symptoms disappeared in 83 teeth, but it resolved only after retreatment using the same procedure in 4 cases. Gingival abscesses and draining sinuses, if present, disappeared after a few days, and the permanent successor erupted without any problems. The mean function time of the primary teeth was 680 days, except for 1 case with congenitally missing permanent teeth. All the cases were evaluated as successful.

Prabhakar et al.[13] evaluated the clinical and radiographic success of endodontic treatment in infected primary teeth using the same combination of drugs as above. They treated 60 teeth in two groups: teeth treated with pulpotomy and teeth treated with pulpectomy. The coronal access was sealed with GIC and reinforced with CR. One-year follow-up showed considerable clinical success in both groups, but a statistically significant difference was observed between them radiographically, wherein the pulpectomy teeth had 83% success compared to 37% for pulpotomies.

Takushige et al.[27] conducted a retrospective clinical study of 360 teeth diagnosed with pulpitis, which

were treated with antibacterial drugs via an indirect or direct pulp capping procedure. Patients with a clinical diagnosis of pulpitis (spontaneous pain, pulp exposure, deep carious lesion) received 3Mix-MP on the pulpal floor of the carious lesion, where softened dentin was intentionally left. The treated lesions were sealed with GIC and then restored with a resin inlay. This therapy was successful in 95% of the 360 cases. Six cases progressed to pulpal necrosis, and the remaining 12 required retreatment using the same 3Mix-MP, subsequently resulting in a good outcome. Recalcification of the softened dentin was evident on postoperative radiographs. These data suggest that 3Mix-MP may be worth evaluating in prospective randomized clinical trials for treatment of pulpitis, including cases of "irreversible" pulpitis.

Nakornchai et al.[17] compared the clinical and radiographic success of 3Mix and Vitapex (NEO Dental International Inc. Federal Way, Wash.) for root canal treatment in 50 pulpally involved primary molars from 37 healthy children, employing a prospective, single-blinded, randomized design. In the control group, a pulpectomy procedure was performed and root canals were filled with Vitapex; in the experimental group, a LSTR pulpotomy was performed. All teeth were restored with SSCs. Both groups demonstrated substantial clinical success at 6 and 12 months, whereas radiographic success at 6 months was 84% for 3Mix and 80% for Vitapex, and at 12 months was 76% and 56%, respectively, which was not statistically significant. Thus, they suggested that 3Mix and Vitapex could be used as root canal treatment agents in pulpally involved primary teeth.

Pinky et al.[26] conducted a study on 28 4- to 10-year-olds with 40 infected primary teeth to evaluate the clinical and radiographic success of endodontic treatment using combinations of antibacterial drugs consisting of 3Mix (group A) and ciprofloxacin, ornidazole, and minocycline (group B). A LSTR procedure similar to that of Takushige et al.[12] was performed and medication cavities were filled with the antibiotic pastes, followed by GIC and SSC placement. Clinical and radiographic evaluations at 3-, 6-, and 12-month intervals showed no statistically significant differences between the groups, suggesting 100% success with these combinations in treating necrosed primary teeth.

Agarwal et al.[7] assessed the clinical efficacy of pulpotomy procedures using Pulpotec (Produits Dentaires SA, Vevey town in Switzerland),[32] a pulpotomy material composed of polyoxymethylene, iodoform, dexamethasone acetate, formaldehyde, phenol, and guaiacol, LSTR

Table 1. Characteristics of LSTR Clinical Studies Reported in Primary Teeth

Clinical studies	Takushige et al.[12] (2004)	Prabhakar et al.[13] (2008)	Takushige et al.[27] (2008)	Nakornchai et al.[17] (2010)	Pinky et al.[26] (2011)	Agrawal et al.[7] (2011)	Trairatvorakul and Detsomboonrat[28] (2012)
Age group (ys)	4-18 years	4-10 years	Not specified†	3-8 years	4-10 years	4-9 years	3-8 years
Primary teeth selected	Upper and lower molars/anteriors	Lower molars*	Not specified†	Upper and lower molars	Lower molars*	Lower molars	Lower molars
Number of teeth (participants)	87 teeth (56 patients)	60 teeth (41 children) Group A: 30 teeth Group B: 30 teeth	360 teeth	50 teeth (37 children) 3 Mix group: 25 teeth Vitapex group: 25 teeth	40 teeth (28 children) Group A: 20 teeth Group B: 20 teeth	60 teeth (34 children) Group 1 (ZOE): 20 teeth Group 2 (Pulpotec): 20 teeth Group 3 (3Mix): 20 teeth	80 teeth (58 children)
Intervention/ technique	Pulpotomy technique	Group A: Pulpotomy technique Group B: Pulpectomy technique	Pulpotomy technique	Pulpotomy technique	Pulpotomy technique	Pulpotomy technique	Pulpotomy technique
Medication cavity	Yes	Yes	No	No	Yes	No	Yes
Ratios of drugs used	1:3:3	1:3:3	1:3:3	1:1:1	1:3:3	1:3:3	1:1:1
Irrigants/cleansers	Phosphoric acid	Saline	Ethylene diamine tetra acetic acid	Sodium chloride	Saline	†	Ethylene diamine tetra acetic acid
Permanent restoration	Glass ionomer cement followed by composite resin inlay	Glass ionomer cement followed by composite resin	Glass ionomer cement followed by composite resin inlay	Glass inomer cement followed by stainless steel crown	Zinc oxide eugenol-glass ionomer cement followed by stainless steel crown after 1 month	Glass inomer cement followed by stainless steel crown (24 hour)	Glass inomer cement/composite resin/stainless steel crown
Follow-up period	68-2,390 days (avg=2 months up to 6.5 years)	12 months (1, 6, 12 mos)	123-2,065 days final follow-up	12 mos (1week, 6 and 12 mos)	12 mos (3, 6, 12 mos)	12 mos (1, 3, 6, 12 mos)	24-27 mos (6, 12, 18-21, and 24-27 mos)

** Not specified clearly, but through case figures and literature it is assumed to be lower molars.* *† Not mentioned in the study.*

using 3Mix, and zinc oxide eugenol (**ZOE**) pulpectomy. Thirty-four children 4- to 9-year-olds with 60 pulpally involved primary mandibular molars were selected and randomly divided into 3 groups, with 20 teeth in each group. Clinical evaluation at 1 month showed only 70% success in the LSTR group (group 3) compared to 100% success in the other 2 groups. The teeth were evaluated clinically and radiographically at 3, 6, and 12 months. By the end of 12 months, the LSTR group displayed a poorer success rate compared to the ZOE pulpectomy group. Thus, the authors concluded that pulpotomy using Pulpotec could be a good alternative for a conventional ZOE pulpectomy compared to LSTR pulpotomy.

Trairatvorakul and Detsomboonrat[28] investigated the success rates of 3Mix in LSTR of 80 primary mandibular molars in 58 children, employing a rigorous evaluation criteria. They also scrutinized whether there were any statistically significant differences in the success rates when using 3Mix-MP among different levels of severity of the preoperative radicular pathology and tooth type. After pulpotomy, medication cavities received 3Mix, which were then sealed with GIC and CR before permanent restoration with a SSC. The patients received a clinical and radiographic assessment every 6 months over a 2-year follow-up period. Internal resorption, increase in inter-radicular radiolucency, and stasis of radiolucent areas contributed to 38 failures (63%). In addition to that, the results showed no statistically significant difference between success rates and the radicular pathology severity. Regarding tooth type, less success was observed in primary first molars than primary second molars. Although LSTR using 3Mix-MP resulted in good clinical success, it had a low radiographic success rate at the 2-year follow-up. Hence, 3Mix antibiotic treatment cannot replace a conventional root canal treatment agent as a long-term therapy.

DISCUSSION

Endodontic therapy plays an important role in removing bacteria and their byproducts and substrates by disrupting and destroying the microbial ecosystem through chemical and mechanical methods.[33] Bacteria present mainly in the root canal and on the superficial layer of the canal wall may be easily removed by conventional endodontic treatment. The bacteria that remain in the deeper layers of root canal dentin, however, might leak out to the periapical region and cause complications.[13] Thus, in recent years there has been a tendency to use more potent antibacterial agents capable of penetrating tissues and controlling infection. As a therapeutic measure, these antibacterial drugs (ciprofloxacin, metronidazole, and minocycline) were applied to sterilize such endodontic lesions in the LSTR technique.[6,12]

The LSTR procedure is simple and requires less chair time by reducing the need for multiple visits.[12] Mechanical instrumentation is not required, which causes too much enlargement of root canals and unnecessary irritation to periapical tissues, especially in teeth with root resorption. In addition to that, the presence of accessory canals and the porosity and permeability of the pulpal floor region in primary teeth indicate a probable connection between pulpal and periodontal tissues. 3Mix might be easily distributed through these regions and induce a sterile zone, which is expected to promote tissue repair. Furthermore, this technique helps to preserve the primary tooth until its exfoliation, reducing the need for unnecessary extraction and placement of a space maintainer.[17]

In vitro research has demonstrated that 3Mix-MP was able to kill bacteria isolated from infected root canals and penetrate through root dentin.[21-23,30] In vivo research has demonstrated that it is effective as a pulpotomy and pulpectomy medicament in treating infected primary teeth (including teeth at varying stages of physiologic root resorption) and irreversible pulpitis.[7,12,13,17,26-28]

In all studies, there was no mention about sample size calculation. Smaller sample size selection was a drawback of these clinical studies,[7,12,13,17,26-28] which might have resulted in a low probability of detecting clinically meaningful treatment effects. An appropriate age group for LSTR is approximately 3 to 8 years old.[17,28] The Takushige et al.[12] study had the longest follow-up time. Their age selection was not appropriate, however, because primary teeth in the 10- to 18-year-old age group (23 of 87 teeth) need not be saved via LSTR, as premolars and maxillary and mandibular canines start their eruption process subsequently.[12] Mandibular molars are preferable, for this type of study as it is easier to identify radiographic pathology and healing more precisely in them. This is important, considering the reduced overlap of permanent mandibular tooth buds and primary molar roots and/or furcations on radiographic examination, which might have attributed to the low success rate in the Trairatvorakul and Detsomboonrat study.[28] These authors excluded teeth with physiologic root resorption greater than one third of the root length, in contrast to Takushige et al.[12] Teeth at this stage will undergo natural exfoliation within a short period of time; thus, their inclusion is questionable. Tooth mobility assessment was not standardized, and how complete disappearance of mobility was quantified was not discussed.

Heterogeneous treatment techniques were observed in these studies. The pulpotomy technique advocated by Takushige et al.[12] demonstrated 100% clinical sucess with few cases requiring retreatment, whereas other LSTR studies[7,17,28] displayed only 75% success without

retreatment. This procedure could be recommended in cases with physiologic root resorption. The LSTR pulpectomy technique (group B) performed by Prabhakar et al.[13] displayed a success rate of approximately 83% radiographic, which is comparable to the success rates of conventional pulpectomy procedures using ZOE (85%) and Vitapex (89%) at 12 months.[34] Thus, complete removal of infected tissue (ie, radicular pulp extirpation) increases the chance for success.[35] In their retrospective clinical study, Takushige et al.[27] performed direct or indirect pulp capping by placing the medicament on overlying dentin without expanding the size of exposure and sealing it with GIC. This pulpitis treatment was termed "LSTR 3Mix-MP save pulp therapy," as the inflamed and infected pulp tissues were not removed but saved in order to restore pulpal functions compared to conventional treatment. They demonstrated good clinical outcome (95% success rate), regardless of the presence of spontaneous pain. Handajani et al.[36] confirmed this histopathologically and stated that disinfection of infected and inflamed pulp tissue—even with spontaneous pain, pulp exposure, or partial necrosis of pulp tissue using 3Mix-MP—might stop pulp destruction and help the survival of pulp tissue when observed 7 days to 19 months after treatment. This means that, by keeping the pulp sterilized, new pulp tissue could be induced.

Sodium hypochlorite is the most commonly used irrigant due to its ability to dissolve necrotic tissue and organic remnants and its superior antimicrobial activity. In researching clinical studies on primary teeth, only Nakornchai et al.[17] was found to have used NaOCL. Others have used saline for irrigation, but they did not mention the reason for its selection over NaOCL.[13,26] Although saline has the ability to flush out debris from the root canals and reduce the number of bacteria in infected root canals by 100 to 1,000 fold, it does not possess superior antimicrobial property like NaOCL. Nevertheless, while considering the disadvantages of NaOCL (such as irritation to periapical tissues and burning of surrounding tissues, which could worsen the situation in primary teeth), saline is preferred, especially in cases selected for LSTR. Additionally, an antibiotic mixture might help eliminate the remaining bacteria.[15,37]

EDTA was preferred, because, in addition to smear layer removal, it acts on the dentinal wall to produce a clean surface and patent dentinal tubules, which would allow antibiotics to penetrate into dentinal tubules.[27-29,38] Hemorrhage was controlled by using NaOCL, which is an effective hemostatic agent. It is also nontoxic, does not interfere with pulpal healing and aids in the removal of clots and stops hemorrhage that compromises pulpal healing.[17]

The antibiotic drugs used in LSTR offer a few disadvantages when used alone. Ciprofloxacin has reduced activity against anaerobes, while metronidazole was ineffective against facultative bacteria and minocycline may cause tooth discoloration (ie, localized minocycline staining of the permanent tooth bud).[17] Therefore, amoxicillin, cefaclor, cefroxadine, fosfomycin, and rokitamycin were tried as a substitute to minocycline and were found to be successful in vitro.[21,22] Further investigation is needed, however, regarding their safety and clinical efficacy. Recently, ornidazole has been tried in place of metronidazole because it has shown longer lasting action with better efficacy and slower metabolism.[26] However, using this drug without any in vitro trials is uncertain when compared to metronidazole.[17,20,26]

The use of systemic antibiotics for local application raises concerns due to its adverse effects. These include allergic reactions, drug side effects, potential for emergence of antibiotic-resistant bacterial strains, risk of developmental anomalies in permanent teeth if used in primary teeth, and cyst formation if the focus of chronic infection is left.[12,16] Nevertheless, the volume of these drugs used as topical agents in LSTR is very small, and there are no reported side effects. LSTR is not recommended in children at risk of infective endocarditis, nor in patients sensitive to these drugs.[17]

MP is an efficient vehicle to carry 3Mix into the dentin through the dentinal tubules to kill bacteria in the pulpal lesions, as those that invade and reside within dentinal tubules may survive if the medicaments introduced into the root canals are not delivered efficiently.[6,39,40]

Conflicting data exist concerning the ratio and proportion of these drug mixtures. Clinical studies[7,12,13,17,26-28] used either 1:1:1 or 1:3:3 ratios of ciprofloxacin, minocycline and metronidazole, respectively. The rationale behind the change in the ratio of the mix is unknown. This could be one of the reasons for the failures seen in the Trairavorakul and Detsomboonrat study,[28] even though they treated teeth with vital pulp and used defined radiographic criteria. Nakornchai et al.[17] also used the same 1:1:1 ratio, but they irrigated with NaOCL, which might have initially decreased the bacterial load. It is debatable whether the concentration of the drugs used in vitro could be adequate in vivo. Further in vivo studies may provide information regarding them. Permanent restoration in most studies was achieved via SSC,[17,26,28] as it is the standard material for extended pulp-treated teeth compared to CR,[12,13,27] which may result in microleakage and treatment failure in the long-term, thus affecting results.

Pinky et al.[26] performed a multi-visit technique, wherein they initially put ZOE on top of the medicament followed by GIC after 15 days, in contrast to other studies where GIC was placed over 3Mix.[12,13] The reaction between eugenol, the remaining pulpal tissues, and 3Mix is not discussed. Moreover, the authors did not mention whether there was any leakage before placement of the SSC at the 30-day recall. These

weaknesses might affect the outcome of the LSTR technique and the quality of the study.

The study by Takushige et al.[12] provided the longest follow-up period (ie, until the teeth exfoliated and the succe-daneous teeth erupted), but their follow-up schedule was random compared to Trairatvorakul and Detsom-boonrat.[28] A major limitation with long-term follow-up studies are that the number of teeth selected for the study preoperatively will get reduced over a period of time, leading to attrition bias. Consequently, in the study by Takushige et al.,[12] only 70 of 87 teeth remained successful after a single treatment. Similarly, out of the 80 primary molars that received treatment by Trairatvorakul and Detsomboonrat,[28] only 60 teeth were available for evaluation at the final follow-up. The reason for dropouts was not mentioned in these studies.

Evaluation criteria are specific to each LSTR clinical study on primary teeth. There are differences in the postoperative clinical success evaluations in these studies, as they were carried out within a different follow-up periods. Based on the radiographic evaluation in LSTR, bone regeneration was considered as success.[28] In the static group, absence of change in discontinuity of the lamina dura or in the size of any radiolucent area was considered "observed" at 6 months and a failure at the 12-month recall.[20] This is concurrent with the American Academy of Pediatric Dentistry guideline[41] on pulp therapy, which states that the radiographically evident pathology of pulpectomized teeth should resolve within 6 months. By contrast, the other studies considered the static bone group a success.[13,17,26] Thus, the definitions of radiographic success in these studies were so diverse that cases considered successful in one study would be classified as failures in the other.

Concern over the hollow tube effect exists in LSTR treated teeth, as their root canals remain unfilled, especially in pulpectomies. It has been thought that an unfilled root canal could be permeated with tissue fluids that become stagnant and eventually form a nidus for infection; whether this actually occurs is yet to be determined.[42,43]

As studies are required to assess the efficacy of this novel treatment modality, Nakornchai et al.[17] compared LSTR with Vitapex and Agrawal et al.[7] compared it with ZOE. In the former study, no significant differences were found between the groups, which was in contrast to the latter study. Furthermore, Agarwal et al.[7] reported cumulative success during follow-up, although they used separate scoring criteria to evaluate clinical and radiographic success. Comparison groups were inappropriate when the pulpotomy technique was compared with a standard pulpectomy, in which removal of the extent of pulp tissue would affect the outcome.

Based on the strengths and weaknesses of each study and by assessing their risk of bias, the Nakornchai et al.[17] study might be judged as of good quality whereas the quality of the Prabhakar et al.,[12] Pinky et al.,[26] and Agarwal et al.[7] studies may be considered fair (having medium risk of bias). The other 3 studies[12,27,28] have no comparison group, although the study by Trairatvorakul and Detsomboonrat[28] could be considered of good quality, as they performed blinded investigations, employed well-defined radiographic criteria, and abided by a uniform follow-up schedule with no attrition bias reported. Takushige et al.[12] had no radiographic follow-up compared to the other studies, and in the study by Takushige et al.[27] there was no mention about age group/teeth included; results were only descriptive without any further statistical analysis. Moreover, both studies[13,27] did not use specific evaluation criteria and regarded retreatment cases as successful. Hence, based on the weaknesses of these studies, they can be assigned as having high risk of bias.[44]

Variation in the success rates of the clinical studies on LSTR was mostly due to the differences in the sample selection, inclusion and evaluation criteria methods, techniques, materials used, data reporting, and outcome bias. Formulation of well-defined clinical and radiographic criteria would help validation and standardization of future studies. Additionally, in order to determine the efficacy of LSTR therapy, well-designed, randomized and unbiased clinical trials, with histological and radiographic evaluations and long-term follow-up are warranted.

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