



Clinical efficacy of local application of sustained-release metronidazole in periodontal therapy

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ABSTRACT

Objective: To update and evaluate the existing scientific evidence in the efficacy of metronidazole as an adjunct as well as an alternative to subgingival debridement/instrumentation.

Methods: Electronic data bases such as Pubmed, Cochrane Central Register of Controlled Trials and Embase were searched for randomized clinical trials (RCTs) that compared the scaling and root planing (SRP) with adjunctive and alternative metronidazole.

Results: This review included twenty-six papers which evaluated the clinical indices such as probing pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP) and/or plaque index (PI). A pair of papers reported the same data at two different papers. Four papers had two test groups. Seven adjunctive studies which used metronidazole in the gel formulation showed statistical significance in reduction of PPD whereas only two studies were able to show a statistical significant gain in CAL. Only one study revealed a significant reduction in BOP. Metronidazole monotherapy has shown a similar reduction in PPD and improvement in CAL to the same extent of SRP.

Conclusions: Taken together it can be delineated that metronidazole may be indicated in patients who have localized persistent and recurrent lesions as an adjunct. However, more RCTs with strict methodological criteria are necessary to come to a firm conclusion.

Clinical significance

Scaling and root planning is pivotal in reducing the bacterial load and mechanical removal of the etiological factors whereas topical metronidazole may be reserved as an adjunct in the management of sporadic pockets of recurrent lesions.

1. Introduction

Periodontitis occurs as a result of dysbiosis of the microorganisms of the dental plaque and the exaggerated immune responses of the host [1]. Putative pathogens implicated in periodontitis include mainly Gram-negative bacteria and spirochetes among others [1]. Periodontitis is a major cause of tooth loss in adults as a result of loss of periodontal attachment apparatus [2]. Several modifiable and genetic factors are also important in initiation and propagation of this disease in which cigarette smoking is considered the most important modifiable risk fac-

tor. Periodontal therapy aims to restore the balance by reducing the putative pathogens leaving flora associated with health intact by reinforcing personal home care, professional prophylaxis, subgingival scaling and root planning (SRP) and surgical pocket reduction. The diagnosis as well as the success of treatment are relied on an array of clinical parameters such as clinical attachment level (CAL), probing pocket depth (PPD), bleeding on probing (BOP), plaque index (PI), gingival index (GI), and radiographic findings [3]. In non-surgical therapy of periodontal disease management, subgingival instrumentation by SRP is considered the gold standard. However, there are several shortcomings to SRP which include lack of effectiveness in certain patient groups [4] and continued periodontal attachment loss in specific sites such as deep periodontal pockets [5] and furcation sites [6] during maintenance phase of therapy [2]. Since SRP is technically demanding and the access and visibility of the pathological sites are limited, complete removal of subgingival biofilm is impossible [7] indicating that other adjunctive methods are in need to increase the efficacy of non-surgical therapies such as SRP. Therefore, other forms of adjunctive therapies such as

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antimicrobials, antiseptics, photodynamic therapy, probiotics and anti-inflammatory drugs have been evaluated [8]. Because of the bacterial etiology, antimicrobials are considered the adjunct of choice for SRP in treating patients having periodontitis.

Several systematic reviews that evaluated the efficacy of different adjunctive drug regimens for chronic periodontitis reported that the conjunction of amoxicillin and metronidazole followed by metronidazole alone seem to be more effective in reducing PPD and gain in CAL [9,10]. Nevertheless, the adjunctive administration of antimicrobials systemically, in the management of patients having periodontitis, has shown more frequent adverse events [10] and a trend in reduction of the magnitude of the clinical benefit over time [9]. This clearly suggests that local administration of antimicrobials may be safer than the systemic administration of antimicrobials [8]. Moreover, local application of antimicrobials has the other added advantages such as better patient compliance, less development of bacterial resistance, ability to administer a higher dose at a more controlled concentrations, and delivery of the active agent in close proximity to the required site [11,12]. In addition, the increase in the efficacy of SRP by adjunctive antimicrobials may limit the requirement of surgical therapy as well as increase the threshold for such therapy especially for deeper pockets [11]. Metronidazole (MET), a nitroimidazole compound, has been demonstrated to be bactericidal to most anaerobic bacteria such as bacteroides, fusobacteria, and treponemes at low concentrations. Another noteworthy fact is that MET exerts bactericidal effects on most Gram-negative anaerobic bacilli without affecting the flora associated with health. Moreover, many studies have demonstrated that development of resistance with anaerobes are rare with MET [13].

1.1. Delivery systems of metronidazole

1.1.1. Irrigation devices/systems

Earlier studies have used various formulations of MET for local delivery such as supragingival and subgingival jet irrigation with 0.05% MET [14] and 0.5% MET in dialysis tubing [15,16]. However, the marginal improvements observed with jet irrigation and dialysis tubing could be due to low concentrations of MET to achieve optimal bactericidal activity and the drug may not have been retained in the sulcus long enough to be effective [13].

1.1.2. Non-biodegradable delivery systems

Acrylic resins saturated with 40% MET had been used to evaluate the efficacy of MET in earlier studies [17]. Though acrylic strips saturated with MET could improve the clinical parameters several shortcomings preclude the use of such slow release devices clinically including dislodgement of the strips from the sulci, irritation to the tissues and the necessity to insert and remove by a clinician [13].

1.1.3. Biodegradable delivery systems

Due to the shortcomings of irrigation and non-biodegradable systems, MET in the form of sustained release gels (Elyzol) and MET impregnated in polymers and collagen (Metrogène) have been developed. Elyzol which is a 25% MET overcomes many of the above-mentioned drawbacks of slow release devices because it is available as a biodegradable gel which becomes semi-solid after contacting with gingival crevicular fluid [18]. Use of other gels such as chitosan has been also reported [19].

1.2. Statistical significance vs. clinical significance

Many systematic reviews and meta-analyses which have evaluated the efficacy of antimicrobials including MET local delivery systems as a monotherapy and as an adjunct to SRP with various durations of follow-up have produced inconsistent outcomes [8,20,21]. Only the systematic review by Pavia et al., [22] has addressed the MET alone and the other reviews analyzed MET as a subgroup. While three meta-analyses

[20,22,23] have shown statistical significance in the reduction of PPD in favor of MET others were unable to demonstrate any statistical significance. Moreover, these systematic reviews used a limited number of studies due to the significant heterogeneity among studies in their systematic reviews. Therefore, the data derived from these studies should be interpreted in terms of statistical as well as clinical significance because high heterogeneity reported in most of the meta-analyses might have overestimated or underestimated the bona fide clinical outcomes of the evaluated pharmacological agents restricting the reliability of such systematic reviews [20]. Statistical significance denotes that a difference between a test and control group occurs due to a cause not by chance. This does not necessarily indicate that the difference is either large or important suggesting that it may not be clinically meaningful [13]. Moreover, change in one parameter (e.g., PPD) does not show the other clinically more benefits (e.g., percentage of sites with ≥ 2 mm PPD reduction or CAL gain) [13]. Though the above-mentioned systematic reviews have shown a statistical significance the magnitude of the effect is rather small. Taken together, it can be stated that it is up to the clinician to decide whether the benefits demonstrated in the form of statistical significance truly reflects the clinical significance based on several factors such as size of the effect, size of the lesions, expected outcome, patient satisfaction, cost and time needed to treat the lesions.

Therefore, the objective of the current study is to review the published literature on the effectiveness of sustained-release local/ topical MET in conjunction with SRP or as an alternative to SRP in patients having chronic periodontitis.

2. Materials and Methods

2.1. Literature search

Human clinical trials published in English language journals were selected by searching electronic databases such as Cochrane Central Register of Controlled Trials, PubMed/Medline and Embase. All articles published until March 2021 were searched against MeSH and free text words. The search strategy for Pub Med (adapted to the other databases) is listed below: (Periodontal Disease OR periodontal disease OR periodontitis) AND (metronidazole) AND (local, OR topical) AND (randomized controlled trials OR clinical trials). The bibliographies of the selected articles and references of systematic reviews were assessed to identify the missing references.

2.2. Selection of studies

Human randomized controlled trials (RCTs) of chronic periodontitis patients older than 18 years with parallel or split-mouth designs were included. Studies exclusively on patients with diabetes, systemic antimicrobials and studies which used MET monotherapy without a control group (SRP) were excluded. For the test groups, patients who have undergone subgingival debridement of the whole mouth or in localized areas at baseline or in repeated sessions in conjunction with MET or MET monotherapy were included. Control groups included received subgingival debridement with a placebo/vehicle or subgingival debridement alone. The principal outcome measures of reduction in PPD, improvement in CAL and reduction in BOP were recorded.

2.3. Data analyses and synthesis of the results

To compare the test and control studies mean changes in PPD, CAL and BOP were extracted from the studies. If the difference in change of clinical indices were not available, they were obtained using baseline and end values as described elsewhere [8,20,24]. In brief, the difference (Δ) was estimated by the formula:

$\Delta\text{PPD} = \text{PPD}_{\text{BL}} - \text{PPD}_{\text{End}}$, where PPD_{BL} was the mean PPD value before treatment and PPD_{End} was the mean PPD after follow-up period. The same formula was applied for the ΔCal and ΔBOP . The variance

(accordingly the SD) was calculated as described elsewhere [8,20, 24] with the formula: $SVar^2 = SVar1^2 + SVar2^2 - 2r.SVar1.SVar2$, where $SVar^2$ is the variance of the difference in PPD value (same for CAL and BOP), $SVar1^2$ is the variance of the mean baseline value, and $Svar2^2$ is the variance of the mean end value, r was the correlation between base line and end whereas $SVar1$ and $SVar2$ were the SDs of the baseline and end values, respectively [8,20,24].

3. Results

The search provided 26 references and a pair of papers reported the same data in two different papers [25,26]. The basic characteristics of the included studies are given in Table 1 which provides an overview of the country the studies were carried out, trial design (split-mouth or parallel) the number of centers such as single or multi center, setting, the periodontal status of the patients included, the product used in each study, sample size, mean age of the population, percentages of females and smokers (%). Studies were categorized into broad groups depending on the drug delivery device such as gel, acrylic strip and irrigation. Table 2 outlines the probe/stent used to measure PPD and CAL, as well as the methodology of the individual studies used to measure other indices such as PI and GI (including BOP).

Adjunctive sustained-release studies compared the outcomes of the SRP alone to that of SRP+MET which delivered MET either in sustained release formulation of gel [18,19,25,27–37], acrylic strip [38] and MET in collagen [39–41]. An adjunctive irrigation study was also carried out [42] which used an irrigation tip fitted to a syringe to deliver the MET subgingivally. The studies aimed to seek the adjunctive or additive effect of MET when combined with the conventional treatment of SRP. Equivalence sustained-release studies compared the clinical outcomes of SRP to that of MET alone in treating patients with periodontitis. The devices used to deliver the agent to the local site included gels [43–47] and acrylic strips [48]. A similar study used an irrigation method [49] which is an electrically operated pump that used a pulsated or non-pulsated waterjet. These studies evaluated the MET as an alternative to SRP in chronic periodontitis. Three MET in gel studies have included both test groups alone and as an adjunct to SRP [33,37,41]. Most of the studies which used MET in gel formulation contained either 25% MET which is marketed as Elyzol, 15% MET in chitosan gel [19] and 15% MET benzoate gel delivered via a tray, whereas the MET delivered in collagen sterile device contains 5% MET [39–41]. The studies which evaluated the adjunctive and alternative effect of MET in polyethyl methacrylate (acrylic) used 50% (w/w) MET [38,48].

Most of the studies used a manual probe to measure the PPD and CAL whereas few studies used a force-controlled computerized probe (Table 2) [25,30–32,35]. Occlusal acrylic stents were used in few studies to facilitate probe positioning and alignment [18,27,29,30,33,35]. Indices used to measure the plaque status, gingival inflammation and bleeding on probing varied among the included studies (Table 2). Few studies provided a description of number of examiners as well as whether the examiners were calibrated prior to data collection (Table 2).

3.1. Scaling and root planning (SRP) alone

The mean reduction of PPD brought by SRP alone was in the range of 0.6 mm – 3.7 mm. Except six studies [19,30,35,41,42,45] all the studies yielded a PPD reduction above 1mm due to SRP alone. Out of six studies mentioned before reduction of PPD of 2 studies were in the neighborhood of 1mm [19,41]. Studies by Radvar et al., [35] and Linden et al., [42] gave a reduction of 0.6 mm whereas it was 0.71 mm by the study of Kinane and Radvar [30]. Two studies revealed high PPD reduction of 3.7 ± 2.1 mm and 3.41 ± 0.74 mm [28,37]. The CAL gain brought by SRP alone in most of the adjunctive studies were about 0.5 mm whereas three studies have a gain of CAL above 2 mm [28,40,37]. The studies which evaluated the SRP in conjunction with MET in acrylic strips showed a reduction of PPD of 1.8 mm - 2.5 mm by SRP alone. The gain of CAL

by SRP alone was in the range of 1.2 mm - 1.6 mm (Table 3). The study which evaluated the effectiveness of 0.5% MET irrigation in conjunction with SRP showed a PPD reduction of 0.6 mm by SRP alone.

3.2. Adjunctive sustained-release studies

Out of 17 adjunctive sustained-release MET in gel formulation studies (Table 1) five were parallel group studies [19,25,27,30,35] whereas the rest were split-mouth studies. Table 3 depicts the relative effect of reduction of PPD, gain in CAL and reduction in BOP of studies which evaluate the adjunctive effect of MET compared to that of SRP alone. Regarding the smoking status of the study population, three studies [19,37,41] used all non-smoker patients, Bergamaschi et al., [27] used all smoker patients, 6 studies used both smokers as well as non-smokers whereas the rest of the studies did not reveal the smoking status of their cohort (Table 1). Out of the 17 adjunctive sustained-release studies which evaluated the efficacy of MET in sustained release gel formulations, seven studies showed statistically significant reduction in PPD (Table 3). The net PPD reduction brought by the drug augmented regimens ranged from 0.18 mm – 1.65 mm. Out of seven parallel group studies only two gave a statistically significant reduction in PPD with a net reduction in the range of 0.22 mm – 0.35 mm [30,35]. Studies which showed a statistically significant net reduction of PPD: 0.5mm at 9 month [29], 0.7mm at 3 month [39], 0.78 mm at 1.5 month [33], 1.65mm at 1 month [41], 0.35mm at 1.5 month [35] and 0.18mm at 9 month [47]. The subgroup analysis of the latter study revealed a net reduction of 0.47 mm of PPD in previously untreated patients ($p < 0.001$). Reduction of PPD between smokers and nonsmokers were not significant [26,36]. Two studies yielded a statistically significant CAL gain: 0.40 mm at 9 month [29] and 0.66 mm at 1.5 month [33]. Only one study revealed a statistically significant reduction in BOP (8%, $p < 0.05$) [47]. Out of 10 studies which did not show a statistically significant reduction in the clinical parameters, four showed a benefit towards test group, four showed similar reduction in both test and control groups whereas two studies demonstrated a benefit towards control [28,37]. The study which used MET in acrylic strip [38] also favored test compared to that of control.

3.3. Equivalence sustained-release studies

Table 3 shows the data of eight studies which used MET in gel device and two studies which used MET in acrylic strip which evaluated the effect of MET as a monotherapy to that of SRP alone. All the former monotherapy studies were split-mouth studies. MET alone without mechanical debridement of the pathological lesions was able to reduce the PPD to the same extent as SRP alone. The reduction of the PPD brought by MET monotherapy was in the range of 0.85 mm - 2.9 mm. Three studies showed a gain of CAL in the range of 0.6 mm – 1.9 mm [33,37,46]. The reduction of BOP brought by MET monotherapy was similar to that of SRP alone [43,44].

3.4. Patient- centered outcomes

Adverse effects associated with adjunctive use of MET were minimal which were included bitter taste, salivation and tooth sensitivity and the latter is most probably due to the local effects of instrumentation. Shooting pain and dental sensitivity were also reported in patients who underwent SRP alone. Reports of adverse effects were not markedly differed between the test and control groups (Table 3).

4. Discussion

The present review identified 17 adjunctive studies which used MET in gel delivery device and one study which used MET in acrylic non-biodegradable device. The included studies showed a marked heterogeneity in relation to the study design, sample size, follow-up period,

Table 1

| Study Reference | Country | Trial design | Centers | Setting | Periodontitisstatus | Product name | Sample size(baseline/End) | Age(mean±SD)range | Sex(% F) | SM(%) |
|--|-----------|--------------|---------|------------|-----------------------|-------------------------------------|---------------------------|-------------------|----------|-------------|
| Metronidazole in gel - adjunctive | | | | | | | | | | |
| Akncbay et al., 2007 | Turkey | parallel | single | university | Mod., Sev.,Ch.P | Chitosan + MET (15%) | 15/15 | 38±6 (31-47) | 53.3 | non-smokers |
| Bergamaschi et al., 2016 | Brazil | parallel | single | university | Ch.P | MET benzoate (15%) | 30/30 | NR | 63.3 | 100 |
| Buduneli et al., 2001 | Turkey | Split-mouth | NR | NR | Ch.P | Elyzol | 18/18 | 41.11±4.9 (35-50) | 55.6 | NR |
| Griffiths et al., 2000 | UK | split-mouth | duel | university | Ch.P | Elyzol | 88/84 | NR (34-71) | 52.3 | 38.6 |
| Hitzig et al., 1997 | France | split mouth | single | university | Ch.P | Metrogène5% MET in collagen device) | 30/30 | 47±3.5 (30-73) | 46.7 | NR |
| Hitzig et al., 1994 | France | split mouth | single | university | Ch.P | Metrogène | 28/28 | (34-73) | 46.4 | NR |
| Kinane&Radvar, 1999 | UK | parallel | single | university | Recurrent P | Elyzol | 83/79 | 45±6.4 | 63.3 | NR |
| Leiknes et al., 2007 | Norway | split-mouth | single | university | NR | Elyzol | 21/21 | 50.3 (33-69) | 52.4 | NR |
| Lie et al., 1998 | Norway | split-mouth | single | university | Mod., Sev.,Ch.P | Elyzol | 18/18 | NR (36-77) | NR | NR |
| Noyan et al., 1997 | Denmark | split mouth | NR | NR | Adult P | Elyzol | 10/10/ | NR (35-51) | 70 | NR |
| Palmer et al., 1998, | UK | parallel | single | university | Mod., Sev., P | Elyzol | 90/84 | NR(35-65) | 52.2 | 33.3 |
| Palmer et al., 1999 | | | | | | | | | | |
| Pandit et al., 2013 | India | Split-mouth | Single | University | Mod-adv chronic | Elyzol | 20/20 | NR | 45 | NR |
| Paul et al., 2014 | India | Split mouth | NR | University | Chronic | Metrogène | 20/20 | NR | NR | non-smokers |
| Radvar et al., 1996 | UK | parallel | single | university | Recurrent P | Elyzol | 67/54 | NR | NR | NR |
| Riep et al., 1999 | Germany | split mouth | single | university | Localized recurrent P | Elyzol | 30/29 | 47 | 41.4 | NR |
| Stelzel&Florès-de-Jacoby, 2000 | Germany | split-mouth | NR | university | Ch.P | Elyzol | 64/59 | 47 (23-70) | NR | 39 |
| Zee et al., 2006 | Hong-Kong | split-mouth | single | university | Recurrent P | Elyzol | 10/10 | 43(29-58) | 40 | non-smokers |

(continued on next page)

Table 1 (continued)

| Study Reference | Country | Trial design | Centers | Setting | Periodontitisstatus | Product name | Sample size(baseline/End) | Age(mean±SD)range | Sex(% F) | SM(%) |
|---|---------|--------------|-----------|------------|---------------------|------------------------|---------------------------|-------------------|----------|-------|
| Metronidazole in gel - monotherapy | | | | | | | | | | |
| Ainamo et al., 1992 | Denmark | Split mouth | Multi(9) | University | NR | Elyzol | 206/199 | 48+/-10(25-75) | 54.37 | 56 |
| Klinge et al., 1992 | Denmark | Split mouth | Multi (4) | University | NR | Elyzol&15%MET | 61/61 | 49+/- 11 | 55.73 | 55.73 |
| Pedrazzoli et al., 1992 | Denmark | Split-mouth | NR | University | NR | Elyzol | 24/24 | 49(27-71) | 54.2 | NR |
| Rudhart et al., 1998 | Germany | Split-mouth | NR | University | Mod-severe Chronic | Elyzol | 46/46 | NR(27-63) | 47.8 | NR |
| Stelzel et al., 1996 | Germany | Split-mouth | Single | University | Mod-sev | Elyzol | 30/30 | 53(36-66) | 33.3 | 20 |
| Metronidazole acrylic strip | | | | | | | | | | |
| Addy et al., 1988 (mono) | UK | parallel | NR | University | chronic | 50% MET in PEM (w/w) | 75/75 | 47.5(27-76) | 50.7 | NR |
| Moran et al., 1990 (mono and adj) | UK | Split mouth | NR | University | Chronic | 50% MET in PEM (w/w) | 69/69 | 47.6(37-58) | 59.42 | NR |
| Metronidazole irrigation | | | | | | | | | | |
| Aziz-Gandour et al. (mono and adj) | UK | Split-mouth | NR | University | chronic | 0.05% MET in irrigator | 23/22 | NR (29-55) | 63.6 | NR |
| Linden et al (adj) | UK | Split-mouth | NR | University | chronic | 0.5% MET in irrigator | 20/19 | NR(24-57) | NR | NR |

F: females; SM: Smokers; MET: Metronidazole; Mono: monotherapy; adj: adjunctive; PEM; polyethyl methacrylate.

| Study reference | PPD/CALProbe and stent | Plaque Index (PI) | Gingival Index (GI) | Number of examiners | Calibrated examiners |
|---|--------------------------|----------------------------|-------------------------------|---------------------|----------------------|
| Metronidazole in gel - adjunctive | | | | | |
| Akncbay et al., 2007 | Williams probe | Silness & Loe | Loe & Silness | 1 | yes |
| Bergamaschi et al., 2016 | UNC 15/stent | Visible plaque index (VPI) | Gingival bleeding index (GBI) | 1 | yes |
| Buduneli et al., 2001 | Periodontal probe | Ainamo and Bay | Saxer and Muhleman | 1 | NR |
| Griffiths et al., 2000 | EN15/stents | NR | NR | 2 | yes |
| Hitzig et al., 1997 | NR | NR | NR | NR | NR |
| Hitzig et al., 1994 | Borodontic | Silness & Loe | Loe & Siiness | NR | NR |
| Kinane & Radvar, 1999 | Florida probe/ stent | Silness & Loe | Lobene et al., 1986 | 1 | NR |
| Leiknes et al., 2007 | Florida Probe | NR | NR | 1 | NR |
| Lie et al., 1998 | Florida Probe | NR | NR | 1 | NR |
| Noyan et al., 1997 | Periodontal probe /stent | Loe & Silness | Silness & Loe | 2 | yes |
| Palmer et al., 1998, 1999 | Florida probe | Dichotomous | Bleeding on probing | 1 | NR |
| Pandit et al., 2013 | NR | Timmerman et al.,1996 | Timmerman et al.,1996 | NR | NR |
| Paul et al., 2014 | Williams probe | Silness & Loe, | Loe & Siiness | NR | NR |
| Radvar et al., 1996 | Florida Probe /Stent | Silness & Loe | Lobene's modified GI | 1 | NR |
| Riep et al., 1999 | UNC 15/ stent | Lange et al.,1977 | Saxer & Mühlemann | 1 | NR |
| Stelzel&Florès-de-Jacoby, 2000 | PCP-12 | NR | Bleeding on probing | NR | NR |
| Zee et al., 2006 | Peri probe/stent | NR | NR | NR | NR |
| Metronidazole in gel - monotherapy | | | | | |
| Ainamo et al., 1992 | PCP 12 | NR | NR | NR | NR |
| Klinge et al., 1992 | PCP-12 | NR | NR | NR | NR |
| Pedrazzoli et al., 1992 | PCP-12 | NR | NR | NR | NR |
| Rudhart et al., 1998 | Florida probe | NR | NR | 1 | NR |
| Stelzel et al., 1996 | PCP-12 | NR | NR | 1 | NR |
| Metronidazole acrylic strip | | | | | |
| Addy et al., 1988 | Williams probe | NR | NR | 1 | NR |
| Moran et al., 1990 | Williams probe | NR | NR | 1 | NR |
| Metronidazole irrigation | | | | | |
| Aziz-Gandour et al. | Williamsprobe | Silness & Loe | Loe & Silness | NR | NR |
| Linden et al., 1991 | William's probe | Silness & Loe | NR | 1 | NR |

smoking status, type of probe used, calibration of examiners, debridement time, disease status, level of severity, depth of the pathological lesions (deep vs. shallow pockets), type of patients recruited (initial vs. maintenance patients), outcome assessment (full mouth vs. partial mouth), statistical unit (patient-based vs site-based) among others. The follow-up periods of the studies ranged from 1 month to 12 months. Out of the adjunctive studies only seven studies showed a statistically significant reduction in PPD out of which 2 were parallel group studies whereas the rest were split-mouth studies. Only two studies showed a statistically significant gain in CAL. The meta-analyses conducted by several researchers have given different weighted mean differences (WMD) in the reduction of PPD that were in the range of 0.06 mm - 0.32 mm (Table 4). The number of studies used in the meta-analyses were limited to 2-7 references which were attributed to the statistically significant heterogeneity among studies [8,41]. All the studies included in the systematic reviews have used studies of Elyzol except two reviews [22,23] which have used a Metrogène study by Hitzig et al., [39] and MET in acrylic strip study by Moran et al., [38].

The salient determinant of successful periodontal therapy is attributed to the detailed thoroughness of the root surface debridement and the patient's standard of oral hygiene rather than the choice of treatment modality. In addition to removal of plaque and calculi, SRP has been shown to initiate a local and systemic host response in curbing the local infection enhancing healing [50]. A study has demonstrated that periodic supportive periodontal therapy (SPT) including SRP along with repeated oral hygiene instruction in patients who are not at high risk of getting periodontal disease was successful in preventing attachment loss and tooth loss subsequent to bone loss as a result of periodontitis [51]. Furthermore, a systematic review which evaluated the effectiveness of SRP in chronic periodontitis [52] has revealed that subgingival debridement including supragingival plaque control is efficacious in PPD reduction and gain in CAL. The weighted mean of attachment gain by SRP in pockets with PPD of 5 mm was 0.64 mm whereas it was 0.37 mm with supragingival plaque control. Similar pattern was observed with

the reduction of pocket depth which were 1.18 mm and 0.59 mm for SRP and supragingival plaque control, respectively [52]. In the present study, we have seen a PPD reduction in the range of 0.6 mm – 3.41 mm, where majority of studies demonstrated a PPD reduction of 1 mm by SRP alone. The differences in the PPD by individual studies could be due to the level of thoroughness of SRP. No restrictions were imposed by Akncbay et al., [19] for SRP and two studies [28,37] have used 9-15 minutes/tooth which suggested a through mechanical instrumentation whereas the rest of studies did not mention the time used for tooth debridement. This was well reflected in the reductions in the PPD observed in these two studies which were 3.41 ± 0.74 and 2.5 ± 2.6 , respectively. In addition, the modest PPD reduction observed with SRP alone could be also due to the 'Hawthorne effect' which make the patients recruited into a clinical trial perform their oral hygiene to their level best than what they do routinely [53].

The frequency of application of the drug is also varied among studies. Studies which evaluated Elyzol were applied twice at baseline and after one week except in the study by Riep et al., [18] who administered the drug every two days for 10 days after baseline application. The Metrogène as well as the MET in acrylic strip was applied one time at baseline. The beneficial effects demonstrated by many studies show a short term follow up in the range of 1-3 months with temporal waning of the magnitude of effect suggesting that antimicrobials (MET) may have to be applied as often as every three months to obtain the long-term beneficial effect in patients who are on maintenance therapy.

Compared to parallel studies split-mouth studies have been shown to reduce the inter-subject variability thus reducing the sample number [8]. However, several investigators queried the possibility of spill-over effect due to the entry of the drug into saliva and reach the other sites making it as an antibacterial mouthwash. Notwithstanding this, a study by Henderson et al., 2002 [54] have clearly demonstrated that split-mouth design does not cause a cross-over effect still making it the trial of choice to evaluate the adjunctive effects of antimicrobials.

Table 3

| Study reference | Study period(m) | Test group PPD reduction (mean±SD) | CAL gain (mean±SD) | Mean BOP reduction | Adverse effects | Control group PPD reduction (mean±SD) | CAL gain (mean±SD) | Mean BOP reduction | Adverse effects | Outcomes with significant difference |
|--|-----------------|--|-----------------------|-----------------------|--|---|-----------------------|-----------------------|-----------------|---|
| Metronidazole in gel - adjunctive | | | | | | | | | | |
| Akncbay et al., 2007 | 6 | 1.48 | 1.0 | NR | NR | 0.94 | 0.4 | NR | NR | No difference |
| Bergamaschi et al., 2016 | 6 | 1.8 | 1.9 | NR | Bitterness, high salivation | 1.8 | 2 | 7 | NR | No difference |
| Buduneli et al., 2001 | 12 | 3.2±0.82 | 2.06±0.59 | | NR | 3.41±0.74 | 2.12±0.53 | | NR | No difference |
| Griffiths et al., 2000 | 9 | 1.5 | 0.8 | 35 | NR | 1.0 | 0.4 | 26 | NR | PPD,CAL |
| Hitzig et al., 1997 | 3 | 2.9±2.89 | NR | NR | NR | 1.7±3.56 | NR | NR | NR | No difference |
| Hitzig et al., 1994 | 3 | 2.1±0.53 | 2.2±1.06 | NR | Pain -1 pt | 1.4± 1.06 | 2.3±1.58 | NR | Pain -1 pt | PPD |
| Kinane &Radvar, 1999 | 6 | 0.93±0.85 | 0.541±0.93 | 37.95 | NR | 0.711±0.84 | 0.537±0.64 | 33.32 | NR | PPD |
| Leiknes et al., 2007 | 6 | 1.9±1.12 | 1.6±2.11 | 38.1 | NR | 1.8±0.57 | 1.0±2.73 | 33.3 | NR | No difference |
| Lie et al., 1998 | 6 | 1.6±1.1 | 0.9±1.9 | NR | NR | 1.1±1.72 | 0.2±2.7 | NR | NR | No difference |
| Noyan et al., 1997 | 1.5 | 2.09 | 1.25 | NR | NR | 1.31 | 0.59 | NR | NR | PPD, CAL |
| Palmer et al., 1998, | 6 | 1.74 | 0.47±0.65 | 12.18±17.9 | NR | 1.68 | 0.51±0.43 | 7.18±21.8 | NR | No difference |
| Palmer et al., 1999 | Smokers | 1.35±0.51 | 0.46±0.25 | 48.4 ±20.8 | NR | 1.12±0.51 | 0.47±0.46 | 47.4 ±12.6 | NR | No difference |
| | NS | 1.97±0.6 | 0.48±0.8 | 40.7 ±17.7 | NR | 1.98±0.44 | 0.53±0.43 | 28.2 ±29.6 | | No difference |
| Pandit et al., 2013 | 3 | 2.7±0.92 | 2.0±3.55 | NR | Bitter taste,sensitivity, dental pain,headache | 1.65±0.74 | 1.7±2.8 | NR | NR | No difference |
| Paul et al., 2014 | 1 | 2.55 ±0.60 | NR | NR | NR | 0.90±0.72 | NR | NR | NR | PPD |
| Radvar et al., 1996 | 1.5 | 0.95±0.6 | 0.57±0.56 | 40 | NR | 0.6±0.5 | 0.26±0.39 | 35.3 | NR | PPD |
| Riep et al., 1999 | 3 | 1.7±0.9 | 1.3±0.8 | 58.6 | NR | 1.7±0.9 | 1.1±0.8 | 48.3 | NR | No difference |
| Stelzel&Florès-de-Jacoby, 2000 | 9 | 1.37 ± 0.48 | 1.01 ±1.11 | 36 | None, bitter taste | 1.19 ± 0.66 | 0.94 ±1.29 | 28 | NR | PPD, BOP |
| Zee et al., 2006 | 12 | 2.7±1.6 | 1.6±1.8 | NR | NR | 3.7±2.1 | 2.7±2 | NR | NR | No difference |

(continued on next page)

Table 3 (continued)

| Study reference | Study period(m) | Test group PPD reduction (mean±SD) | CAL gain (mean±SD) | Mean BOP reduction | Adverse effects | Control group PPD reduction (mean±SD) | CAL gain (mean±SD) | Mean BOP reduction | Adverse effects | Outcomes with significant difference |
|---|-----------------|--|---------------------|--------------------|---|---------------------------------------|--------------------|--------------------|-----------------------------------|--------------------------------------|
| Metronidazole in gel - monotherapy | | | | | | | | | | |
| Ainamo et al., 1992 | 6 | 1.3 | NR | 32 | Bitter taste | 1.5 | NR | 39 | Shooting pain, Dental sensitivity | No difference |
| Klinge et al., 1992 | 3 | 1.2 ^a 1.0 ^b 1.2 ^c | NR | 23 24 29 | Unpleasant taste, Vomiting, gingival tenderness | 1.3 | NR | 29 | Gingival tenderness | No difference |
| Paul et al., 2014 | 1 | 0.85±0.67 | NR | NR | NR | 0.90±0.72 | NR | NR | NR | No difference |
| Noyan et al., 1997 | 1.5 | 1.41 | 0.63 | NR | NR | 1.31 | 0.59 | NR | NR | No difference |
| Pedrazzoli et al., 1992 | 6 | 1.14 | NR | NR | NR | 0.88 | NR | NR | NR | No difference |
| Rudhart et al., 1998 | 6 | 1.6±1.0 | 0.7±2.2 | NR | NR | 1.6±0.9 | 0.5±1.9 | NR | Shooting pain, Dental sensitivity | No difference |
| Stelzel et al., 1996 | 6 | 1.32 | NR | NR | Unpleasant taste, gingival pain | 1.5 | NR | NR | Periapical lesions | No difference |
| Zee et al., 2006 | 12 | 2.9±1.7 | 1.9±1.9 | | | 3.7±2.1 | 2.7±2 | | | No difference |
| Metronidazole acrylic strip | | | | | | | | | | |
| Addy et al., 1988 | 3.5 | 2.7±3.3 | 2.6±3.4 | NR | NR | 1.8±3.14 | 1.2±4.1 | NR | NR | No difference |
| Moran et al., 1990 | 3 | Adj: 3.4±1.6 Mono: 2.8±1.8 | 1.9±3.05 2.3±2.8 | NR NR | NR | 2.5±2.6 | 1.6±3.14 | NR | NR | No difference |
| Metronidazole irrigation | | | | | | | | | | |
| Linden et al., 1991 | 3 | 1.0 ±0.22 | NR | 0.9±0.28 | NR | 0.6±0.42 | NR | 0.7±0.28 | NR | No difference |

PPD, probing pocket depth; CAL, Clinical attachment level; BOP, bleeding on probing; SD, standard deviation; NR, Not reported.

^a Elyzol

^b : (15%)x1/wk

^c : (15%)x2/wk

| Systematic review reference | Study duration(months) | References used in the reviews | WMDPPD | WMDCAL | WMDBOP | Outcomes with significant difference |
|-----------------------------|------------------------|---|--------------------|-------------------|--------------------|--------------------------------------|
| Hanes and Purvis 2003 | >3 | Riep et al., 1999 Stelzel 2000 | 0.06 | 0.07 | NR | No difference |
| Pavia et al., 2004 | 3 | Hitzig et al., 1994 (only 3 months) Lie et al., 1998 | 0.30 (P<0.001) | 0.28 (P<0.001) | NR | PPD, CAL |
| | 6 | Griffiths et al., 2000 Kinane &Radvar, 1999 | 0.29 (P<0.001) | 0.29 (P<0.001) | NR | PPD, CAL |
| Bonito et al., 2005 | >6 | Griffiths et al., 2000 Kinane&Radvar, 1999 Lie et al., 1998 Palmer et al., 1998 Riep et al., 1999 Stelzel 2000 Moran et al., 1990 | 0.32 (p<0.0001) | 0.12 (p=0.03) | NR | PPD, CAL |
| Matesanz-Pérez et al., 2013 | >1 | Kinane&Radvar, 1999 Riep et al., 1999 Palmer et al., 1999 | 0.157 (p=0.035) | 0.008 | 4.475 (p=0.000) | PPD, BOP |
| Smiley et al., 2015 | >6 | Palmer et al., 1999 (NS) | | 0.26 | NR | Compared smokers and non-smokers |
| | | Palmer et al., 1999 (SM) | | -0.04 | NR | |
| Herrera et al., 2020 | 6-9 | Kinane&Radvar, 1999 Leiknes et al., 2007 Lie et al., 1998 Palmer et al., 1999 Stelzel 2000 | 0.14 | 0.035 | 4.315 | No difference |
| | >12 | Buduneli et al., 2001 | -0.21 | -006 | NR | No difference |
| Oileng et al., 2020 | >6 | Griffiths et al., 2000 Leiknes et al., 2007 | 0.21 | 0.5 | NR | No difference |

WMD: weighted mean difference; PPD: probing pocket depth; CAL: clinical attachment level; BOP: bleeding on probing; NR: not reported; NS: non-smokers; SM: smokers.

Type of the probe and the force exerted by it have also been shown to affect the final outcome [55]. According to the review by Al Shayeb et al., 2014 [55] systematic error can be avoided by calibration and blinding of the study whereas random error can be reduced by large sample size [56], appropriate and concurrent control group, and randomized allocations. However, the studies included in this review and other systematic reviews do not use large sample size except in few studies and the allocation was not reported in many studies. However, split-mouth design of many studies provided an appropriate and concurrent control group. Several studies have reported that using automated probes such as Florida probe enabled even non-experienced examiners produce accurate and reproducible data [56]. Few of the studies included in the present review have used Florida probe to measure the clinical outcomes.

Though few meta-analyses have demonstrated a statistically significant net reduction in PPD, however, the difference between test and control groups seems modest and in the neighborhood of 0.5 mm. If the clinician feels that the average improvement of PPD around 0.5 mm is clinically important then, most of the adjunctive studies have shown that MET is effective as an adjunctive to SRP. Studies have demonstrated that organized structure of biofilms are able to prevent the diffusion and inactivation of pharmacological agents suggesting that prior removal of plaque and calculi are mandatory before using antimicrobial agents. Therefore, the available antimicrobials should be used as an adjunctive not as a replacement to SRP. However, it should be emphasized that the administration of a local adjunctive should be targeted to the lesions which do not respond to the conventional treatment of SRP [23]. Adjunctive therapy may also be considered for refractory patients for those who could not be treated by surgical intervention due to medical condition of the patient and for those who resist such treatment. As suggested by Herrera et al., [8]: the adjunctive use of locally delivered subgingival antimicrobials results in statistically significant benefits in terms of PPD

reduction and (only short-term) CAL gain, no increase in adverse effects or differences in PROMS, and no significant adjunctive long-term effect. Herrera's [8] long-term data did not show significant improvement of CAL for any product. Data on BOP and pocket closure were insufficient. Sanz et al., [57] in the EFP clinical practice guidelines claim that specific locally administered sustained-release antibiotics as an adjunct to subgingival instrumentation in patients with periodontitis may be considered, but in these antibiotics (Arestin, Aridox and Ligosan) MET is not included.

Taken together it can be stated that the literature published so far is inconsistent to define a clinically important PPD reduction or CAL gain due to the adjunctive use of MET. Therefore, clinicians should pay heed for factors such as time to treat, cost, adverse effects, patient satisfaction, localized nature of the disease before deciding on the adjunctive use of MET to conventional therapy of SRP. More RCTs with strict methodological criteria are necessary to come to a firm conclusion on the use of MET as an adjunctive due to the high heterogeneity and high risk of bias shown by the articles included in many systematic reviews.

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The authors declare that they do not have any conflict of interest.

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