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Efficacy of Local Drug Delivery Agents as an Adjunct to Scaling and Root Planing for Treating Furcation Defects in Chronic Periodontitis - A Systematic Review Protocol

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ABSTRACT- *Periodontal disease is a chronic inflammatory disease initiated by dental plaque. Periodontitis affects the periodontium as a whole. It leads to destruction of alveolar bone and ultimately tooth loss. Chronic periodontitis affects the root trunk of multirooted teeth commonly leading to furcation defect. Pharmacologic management of chronic periodontitis is used as an adjunct to conventional scaling and root planing (SRP). It includes chlorhexidine mouth rinses, subgingival irrigation and local drug delivery agents. Potential therapeutic agents such as non-steroidal anti-inflammatory drugs, chemically modified tetracyclines, and bisphosphonates to treat bone resorption are well documented in periodontal literature. However, the role of local drug delivery agents (LDD) as an adjunct to scaling and root planing needs further exploration and research. The aim of this systematic review will be to determine the efficacy of the currently available local drug delivery agents as an adjunct to scaling and root planing for the treatment of furcation defects in chronic periodontitis*

Objectives

To assess the effect of LDD agents as an adjunct to SRP in furcation defects.

Search Methods

We will search PUBMED and CENTRAL, EMBASE without language restrictions up to March2019. We will also search for ongoing studies in trial registers, perform handsearching, check bibliographic references of relevant articles to seek potentially relevant research. We won't apply any restrictions on language, date, or publication status.

Selection Criteria

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We will include randomised controlled (parallel-group or cross-over) trials comparing use of LDD as an adjunct to SRP in chronic periodontitis patiemts with furcation involvement.

DATA COLLECTION AND ANALYSIS

Three review authors will independently assess studies for eligibility. Three review authors will then extract data and assess the risk of bias for individual studies using standard Cochrane methodology. The evidence will be assessed using GRADE and create 'Summary of findings' tables.

I. BACKGROUND

DESCRIPTION OF THE CONDITION

Periodontitis is the most prevelant chronic inflammatory disease of oral cavity in the population, characterized by inflamed gingiva and loss of connective tissue attachment between the tooth and its surrounding alveolar bone[(1)]. The World Workshop for the Classification of Periodontal Diseases and Conditions , 1999 has identified 3 types of periodontitis based on specific etiologic formulation as chronic periodontitis, aggressive periodontitis, and periodontitis as a manifestation of systemic disease. The pathogenesis of periodontal disease manifests as chronic inflammatory process caused by bacterial exposure in the form of "dental plaque" and host immune-inflammatory response leading to the destruction of connective tissue and bone. The major etiology behind the destruction of investing and supporting periodontal tissue is the induced production and activation of lytic enzymes and stimulated osteoclastogenesis[(2)]. This affects the supporting apparatus of the teeth, leading to migration of the epithelial attachment in the apical direction and cause resorption of connective tissue and alveolar bone. Untreated and unresolved bone destruction can often reach to the area of root separation, exposing the area to microbial colonization creating "furcation involvement". The degree of furcation involvement is a clinical indicator to predict the severity of periodontal tissue breakdown and to determine the attachment and tooth loss in multirooted teeth.

DESCRIPTION OF THE INTERVENTION

The management of furcation defect ranges from nonsurgical periodontal therapy, such as scaling and root planing alone or scaling and root planing plus systemic or local anti-inflammatory or antimicrobial agents, to surgical flap debridement, hemisection, root resection, and regenerative treatment as the most recent advanced therapy.[(3)] As an adjunct to therapy, subgingival drug delivery may increase the efficacy for a beneficial microbial shift and decrease the need for periodontal surgery. For the treatment of new chronic periodontitis cases and recurrent cases of periodontitis, a mechanical non-surgical debridement is always used and the added value of a subgingival drug to scaling and root planing proves as a boon for improving the periodontal health of the patients.

HOW THE INTERVENTION MIGHT WORK

A local route of drug delivery attains its higher concentrations of an antimicrobial property in subgingival sites due to its onsite application as compared with a systemic drug regimen which shows systemic effects on the other hand.Potential therapeutic agents such as nonsteroidal anti-inflammatory drugs, chemically modified tetracyclines, and bisphosphonates (BPs) to treat bone resorption are well documented in periodontal literature and hoping this therapy as a boon for treating furcations in compromised periodontal condition can provide a

new wave of adjuvant pharmacologic agents for periodontal regeneration and osteogenic induction[4]. Fiorellini and Paquette (1992) pointed out that with a restricted therapeutic effect on the periodontal microenvironment, we can achieve a high MIC for a prolonged period of time. This high concentration of antimicrobial agent may affect micro-organisms even in undisturbed biofilms[5].

WHY IS IT IMPORTANT TO DO THE REVIEW

Antimicrobial properties of local drug delivery agents have the therapeutic potential in the management of periodontal diseases .Also the use of local drug delivery agents as an adjunct to scaling and root planning helps in achieving statistically significant modest gains in the attachment level and reduction in pocket depth , but this is not clinically substantial and meaningful[6]. However, efficacy of local drug delivery agents as an adjunct to non surgical periodontal therapy, scaling and root planning ,have not been systematically reviewed. There is a need to synthesise the evidence for patients, practitioners and policy makers to determine the overall effectiveness of local drug delivery agents in furcation defects in chronic periodontitis patients. Therefore, systematic evaluation of the role of local drug delivery agents in furcation defect is necessary.

II. METHODOLOGY-

Search methods for identification of studies

We will search PUBMED, CENTRAL, EMBASE database without language restrictions. We will use Medical subject headings (MeSH) or equivalent and textword terms. We will search the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), National clinicaltrials.gov (www.clinicaltrials.gov). Additionally, we will check the reference lists of reviews, retrieved articles for additional studies, and performed citation searches on key articles.

Criteria for considering studies for this review

Types of studies

We are planning to include randomised controlled trials (RCTs) with open or blinded assessment of outcomes. We will require full journal publication with the exception of extended abstracts of otherwise unpublished clinical trials. We will exclude short abstracts (usually meeting reports), non-randomised studies, studies of experimental pain, studies done on animal models, case reports, and clinical observational studies. Only articles published in English will be included. Details of all the studies used will be summarized in the table named “summary of articles”.

Types of participants

Systemically healthy patients aged from 30- 50 years and clinical diagnosis of chronic periodontitis having furcation involvement will be included irrespective of age, gender and race.

TYPES OF OUTCOME MEASURES

Primary outcome will comprise-

1. Mean of the indices [Plaque index (PI) Gingival index] measured at 6 months.
2. Mean of relative vertical clinical attachment loss (RVCAL) measured at 6 months.
3. Mean of relative horizontal clinical attachment loss (RHCAL) measured at 6 months.

Secondary outcome

1. Mean of periodontal pocket depth (PPD) measured at 6 months.
2. Mean of bone defect depth and bone defect fill measured at 6 months.
3. Mean of bone defect angle measured at 6 months.
4. Mean of tooth specific clinical attachment (Ts CAL) measured at 6 months.

Collection of Data and its analysis

Selection of studies-

The Rayyan online screening tool [7] will be used for screening the search results independently by three review authors (VB, RO, VS) and articles will be retrieved. The eligibility of each study will be determined by briefing the abstracts of each study identified by the search. The studies that won't clearly satisfy the inclusion criteria will be eliminated by review authors. Full copies of all the remaining studies will be obtained. The full texts of these studies will be independently screened to select relevant studies by primary reviewers (RO, VS, SB). If there will be any missing data or information in the studies that will affect our study selection criteria then the respected authors will be contacted either by telephone or email and the necessary clarification for the information will be done. In situations of disagreement or dispute, a fourth author will be asked for a judgment (SB). Anonymisation of the studies will not be performed before assessment. We won't apply any language restrictions in the selection of studies. A "PRISMA flow chart" will be added in the full review to show the detailed status of all identified studies [8] as recommended in "Part 2, Section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* [9]*"*. Irrespective of the reporting of outcome data, studies will be included in this review.

Data extraction (selection and coding)

Three reviewers (RO, VS, SB) will get the data extraction done from "included studies" using a pre-defined data extraction form and will be presented in "Characteristics of Studies Table". Data will be extracted in terms of type of study, details of participants, details of intervention, outcomes reported. Third reviewer (VB) will resolve the discrepancy amongst the primary reviewers. The discrepancy "risk of bias assessment" will be resolved by fourth reviewer (MNK).

Risk of bias (quality) assessment

Risk of bias(RoB) will be assessed independently by the three reviewers (VB, RO, VS) from each included study using the Cochrane domain based, two part tool as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions[10]. The discrepancy among the primary reviewers will be resolved by fourth reviewer (MNK). We will assess the RoB under the domains of :

1. Sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.

7. Other bias, for example, baseline imbalance.

Strategy for data synthesis

The process of meta-analysis will be done only if there are sufficient similarities between participants, interventions, comparisons and outcomes. Accordingly further steps will be undertaken using "RevMan2014", the "statistical package manager" for meta-analysis provided by the "Cochrane Collaboration". Fixed-effect model will be undertaken for meta-analysis following the specific requirements of data which should be sufficient and homogeneous with comparable outcomes. If "statistical heterogeneity" depicting "I^2 greater than, or equal to 70%" is found, then we intend to identify the sources of heterogeneity, explore the cause of heterogeneity through subgroup analysis, and undertake "subsequent meta-analysis" following a "random-effects model". When metaanalysis seems inappropriate, pooling of the obtained results from included studies will not be done rather will be presented as qualitative description of these studies with supporting tables.

Analysis of subgroups or subsets

We will take the subgroups on the basis of type and duration of the intervention given.

Unit of analysis issues

Individual participant will be considered as the "unit of analysis" in parallel-group RCTs. The "cross-over" designed trials are incorporated into "meta-analysis" by following the approach suggested by Elbourne [(11)]. Such trials will be incorporated by taking measurements from "experimental intervention periods" and from "control intervention periods" respectively and analysing these assuming it as a "parallel group trial" of intervention versus control.

Dealing with missing data

According to the number of studies available we will plan to execute an intention-to-treat analysis. Further information from the authors or manufacturers will be asked if the published data are found to be incomplete, missing or inconsistent with RCT protocols. Authors will be contacted by email if the included studies has not reported regarding the outcome measures of interest, description regarding randomization and intention-to-treat analysis or had missing data in the study outcome.

Assessment of heterogeneity

We are planning to assess the clinical heterogeneity by using Chi2 test (P value < 0.10 for statistical significance) and use the I2 statistic to quantify the heterogeneity in the outcomes of the included studies. Heterogeneity will be regarded as considerable if I^2 is more than 75%; substantial if it is between 50% and 90%; moderate if it is between 30% and 60% and mild if it is less than 40% [(12)] If statistical heterogeneity with I^2 greater than, or equal to 50% is identified; then possible causes by prespecified subgroup analysis will be explored , and random-effects model will be applied and reported.

Assessment of reporting biases

If the included studies would be 10 or more than 10 ; we will plan to conduct a funnel plot test for any asymmetry and evidences regarding reporting bias will be assessed.

Data synthesis

We plan to undertake a meta-analysis only if participants, interventions, comparisons and outcomes of the included studies were judged to be sufficiently similar to reveal an answer that has clinical significance and relevancy. We planned to execute the meta-analysis using "RevMan 2014", statistical package provided by the Cochrane Collaboration for analysis. If statistical heterogeneity showing I^2 greater than, or equal to 50% will be detected, then the sources of the heterogeneity will be identified and the subsequent meta-analysis using a random-effects model will be performed.

Summary of findings tables

We plan to include "Summary of findings" (SoF) tables as per the PaPaS author guide [13] and as recommended in the "*Cochrane Handbook for Systematic Reviews of Interventions"* [9]. The SoF tables depicting the following comparisons for all of the primary outcomes of the studies will be presented as:

1. Mean of the indices [Plaque index (PI): An index estimating oral hygiene status by measuring the level of dental plaque that occurs in the areas of tooth surface adjacent to the gingival margin irrespective of the type of index.
2. Mean of Gingival index (GI): An index for assessing the severity and quantity of gingival inflammation irrespective of the type of index.
3. Mean of relative vertical clinical attachment loss (RVCAL): Distance from "cemento-enamel junction" to the base of pocket measured using a "fixed reference point".
4. Mean of relative horizontal clinical attachment loss (RHCAL): Distance from "cemento-enamel junction" to the base of pocket measured using a "fixed reference point".

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