Original Article

Local Drug Delivery Agents As Adjunct To Conventional Therapy For Furcation Defects: A Systematic Review And Meta-Analysis.

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ABSTRACT

Background

Dental plaque is the etiologic factor for various periodontal problems. It is a chronic inflammatory disease initiated by dental plaque. Chronic periodontitis affects the root trunk of multirooted teeth. Pharmacologic management is used as an adjunct to conventional scaling and root planing (SRP). It includes chlorhexidine mouth rinses, subgingival irrigation and local drug delivery (LDD) agents. Potential therapeutic agents such as non-steroidal anti-inflammatory drugs, chemically modified tetracyclines and bisphosphonates to treat bone resorption are well documented in literature. However, the use of LDD agents needs further exploration. To determine the efficacy of LDD agents as an adjunct to SRP for treating furcation defects in chronic periodontitis.

Materials and Methods

Protocol was registered in prospero, no: CRD42019145936. Databases searched were PUBMED, COCHRANE, up to March 2019, without language restrictions. Studies in trial registers, handsearching, bibliographic references of relevant articles were also checked. Data collection and analysis was done by individual authors. Three review authors independently assessed studies for eligibility. Three review authors then extracted data and assessed the risk of bias for individual studies using standard Cochrane methodology. We assessed the evidence using GRADE and created 'Summary of findings' tables.

Results

Meta-analysis was done including five studies (Pradeep2012, Pradeep 2013, Gupta2019, Singhal2017, Garg2016,) It supported that local drug delivery as an adjunct to scaling and root planing is more effective than scaling and root planing alone. We included five studies reporting data from 390 participants, aged 18+ years, comparing local drug delivery agents plus "scaling and root planing" with "scaling and root planing" with placebo. Studies reported data on periodontal parameters like pocket depth, gingival bleeding, clinical attachment loss. Indices including plaque index and gingival index. Ipshita2018 used and compared both allopathic and herbal agent hence was not included for meta-analysis. Due to the differences in the time of reporting of the included studies, all of them were not included for meta-analysis. Meta-analysis was done including five studies (Pradeep2012, Pradeep 2013, Gupta2019, Singhal2017, Garg2016,) It supported that the use of local drug delivery as an adjunct to scaling and root planing is more effective than scaling and root planing alone.

Conclusion

Use of LDD agents as adjunct to SRP is more effective in treating furcation defects.

Keywords

Local Drug Delivery Agents, Chronic Periodontitis, Furcation Defects, Systematic Review, Meta-analysis

Clinical relevance

"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. 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. The role of "local drug delivery agents" as an added therapy to scaling and root planing, on the other hand,

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Bangladesh Journal of Medical Science Vol. 24 No. 01 January'25

DOI:https://doi.org/10.3329/bjms.v24i1.78764

requires more investigation and development. The goal of this systematic review is to see how effective local drug delivery agents are in addition to scaling and root planing for treating furcation defects in chronic periodontitis.

INTRODUCTION

Periodontitis is the most common chronic inflammatory illness of the oral cavity, marked by inflamed gingiva and the loss of connective tissue attachment between the tooth and its surrounding alveolar bone[1]. Chronic periodontitis, aggressive periodontitis, and periodontitis as a manifestation of systemic disease were classified as three forms of periodontitis by the World Workshop for the Classification of Periodontal Diseases and Conditions in 1999. Periodontal disease is characterised by a chronic inflammatory process triggered by bacterial exposure in the form of "dental plaque" and a host immune-inflammatory response that results in the destruction of connective tissue and bone. The induced synthesis and activation of lytic enzymes, as well as accelerated osteoclastogenesis, are the primary causes of periodontal tissue loss[2]. This disrupts the teeth's supporting mechanism, causing epithelial attachment migration in the apical direction and connective tissue and alveolar bone resorption. Untreated and unresolved bone degeneration can often reach the root separation area, exposing it to microbial colonisation and resulting in "furcation involvement." In multirooted teeth, the degree of furcation involvement is a clinical sign for predicting the severity of periodontal tissue breakdown and determining attachment and tooth loss.

Nonsurgical periodontal therapy, such as SRP alone or SRP plus systemic or local anti-inflammatory or antibacterial drugs, to surgical flap debridement, hemisection, root excision, and regenerative treatment as the most recent advanced therapy, are all options for treating a furcation defect[3]. Subgingival medication distribution as an adjuvant to therapy may improve the efficacy of a favourable microbial shift and reduce the need for periodontal surgery. A mechanical non-surgical debridement is always utilised for the treatment of new chronic periodontitis cases and recurrent cases of periodontitis, and the addition of a subgingival medication to scaling and root planing shows to be a boon for improving the periodontal health of the patients.

The use of 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. Therefore, their use as adjuvant pharmacologic agents for periodontal regeneration and osteogenic induction may open-up newer avenues in treating furcations[4]. When compared to a systemic medication regimen, a local route of drug delivery can achieve 100-fold higher concentrations of an antibacterial agent in subgingival locations. When compared to repeated systemic doses of tetracycline-HCl, which can only provide tetracycline levels of 4-8 pg/ml in gingival crevicular fluid after 10 days, local placement of a tetracycline-releasing ethylene vinyl acetate monolithic fibre can yield tetracycline concentrations in excess of 1300 Fg/ml in gingival crevicular fluid after 10 days[5]. When compared to a systemic treatment regimen, a local route of drug delivery not only achieves higher concentrations of an antibacterial property at the site of delivery, but also reduces systemic effects. We can attain a high MIC (Minimal Inhibitory Concentration) for a long time with a restricted therapeutic effect on the periodontal microenvironment, according to Fiorellini and Paquette (1992). Even in undisturbed biofilms, this high concentration of antimicrobial substance may impact bacteria[6].

Antimicrobial properties of local drug delivery agents have the therapeutic potential in the management of periodontal diseases. In addition, when used in conjunction with scaling and root planing, local medication delivery agents can help provide statistically significant minor gains in attachment level and pocket depth, although they are not clinically significant and useful[7]. Despite the fact that an increased percentage of deep sites may demonstrate an improvement, LDD cannot be utilised consistently in combination with SRP due to the low therapeutic benefit. Patients who may benefit the most from LDD should be identified through prospective multicenter studies that incorporate risk factors for disease development. The controversies are limited for non-responding sites or recurrent pockets, because a combined SRP and LDD may eliminate the necessity for surgery. However, the effectiveness of local medication delivery agents as a supplement to nonsurgical periodontal therapy, like as scaling and root planing, has not been thoroughly investigated. To establish the overall effectiveness of local medication delivery agents in furcation deficiencies in chronic periodontitis patients, it is necessary to synthesise the

research for patients, practitioners, and policymakers. As a result, a thorough examination of the involvement of local medication delivery agents in the furcation defect is required.

METHODOLOGY

Protocol Development

The review protocol has been registered in Prospero **(CRD42019145936).** The protocol used to assess the methodologic quality of this systematic review was PRISMA STATEMENT, which can be accessed at *www.prisma-statement.org/* (a tool to evaluate systematic reviews)[8]. It is an evolution of the original QUOROM guideline for systematic review which enables judgement of systematic reviews of both randomized and non-randomized control trials[9].

Focused Question

The question this systematic review is attempting to answer is: Whether local drug delivery agents used as an adjunct to scaling and root planing is better than only scaling and root planing alone for treatment of furcation defects in chronic periodontitis, observed in adults ≥18 years of age based on the body of evidence gathered from existing literature of both randomized and non-randomized clinical trials?

Methods for locating research in the database

The International Prospective Register of Systematic Reviews (PROSPERO) was searched to ensure that no systematic review tackles the same topic which was being undertaken as of April 8, 2019, then a record of this study was submitted on the same day to PROSPERO, indicating that a systematic review was in progress[10]. This systematic review was conducted from May 13, 2019 to November 14, 2020. Articles dated before May 13, 2019 that conformed to the inclusion criteria were included in the analysis.

Without any language constraints, we searched the "PubMed database". Medical topic headings (MeSH) or equivalent terms. The textword terms, were also employed. We looked through the "meta Register of Controlled Trials (mRCT) (www.controlled-trials.com/mrct)", as well as the "National Clinical Trials.gov database (www.clinicaltrials.gov)". We also searched through review "reference lists", retrieved articles for new investigations, and conducted citation searches on key articles.

"Criteria for considering studies for this review"

"Types of studies"

We intended to use randomized controlled trials (RCTs) that assessed outcomes in an open or blinded manner. With the exception of lengthy summaries of otherwise unreported clinical trials, we required full journal publication. Short abstracts (typically meeting reports), non-randomized research, experimental pain studies, animal model studies, case reports, and clinical observational studies were all omitted. Details of the studies included from various sources are given in figure 1 (Prisma flow diagram)

Types of participants

Systemically healthy subjects, aged 30- 50 years and diagnosed to have chronic periodontitis with furcation involvement were included, irrespective of age, gender and race.

TYPES OF OUTCOME MEASURES

Primary outcomes

1. Changes in relative vertical clinical attachment loss (RVCAL) measured at baseline, 3 months and 6 months.
2. Changes in relative horizontal clinical attachment loss (RHCAL) measured at baseline, 3 months and 6 months.

Secondary outcomes

1. Changes in periodontal pocket depth (PPD) measured at baseline, 3 months and 6 months.
2. Change in tooth specific clinical attachment (TsCAL) measured at baseline, 3 months and 6 months.
3. Change in the indices [Plaque index (PI) Gingival index (GI)] measured at baseline, 3 months and 6 months.

Search methods for identification of studies

We searched "Medline via PubMed, Cochrane, database without language restrictions. We used Medical subject headings (MeSH) or equivalent and textword terms. We searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), National clinicaltrials.gov (www.clinicaltrials.gov). Additionally, bibliography of the relevant references was checked, retrieved articles for additional studies, citation searches on key articles, Manual

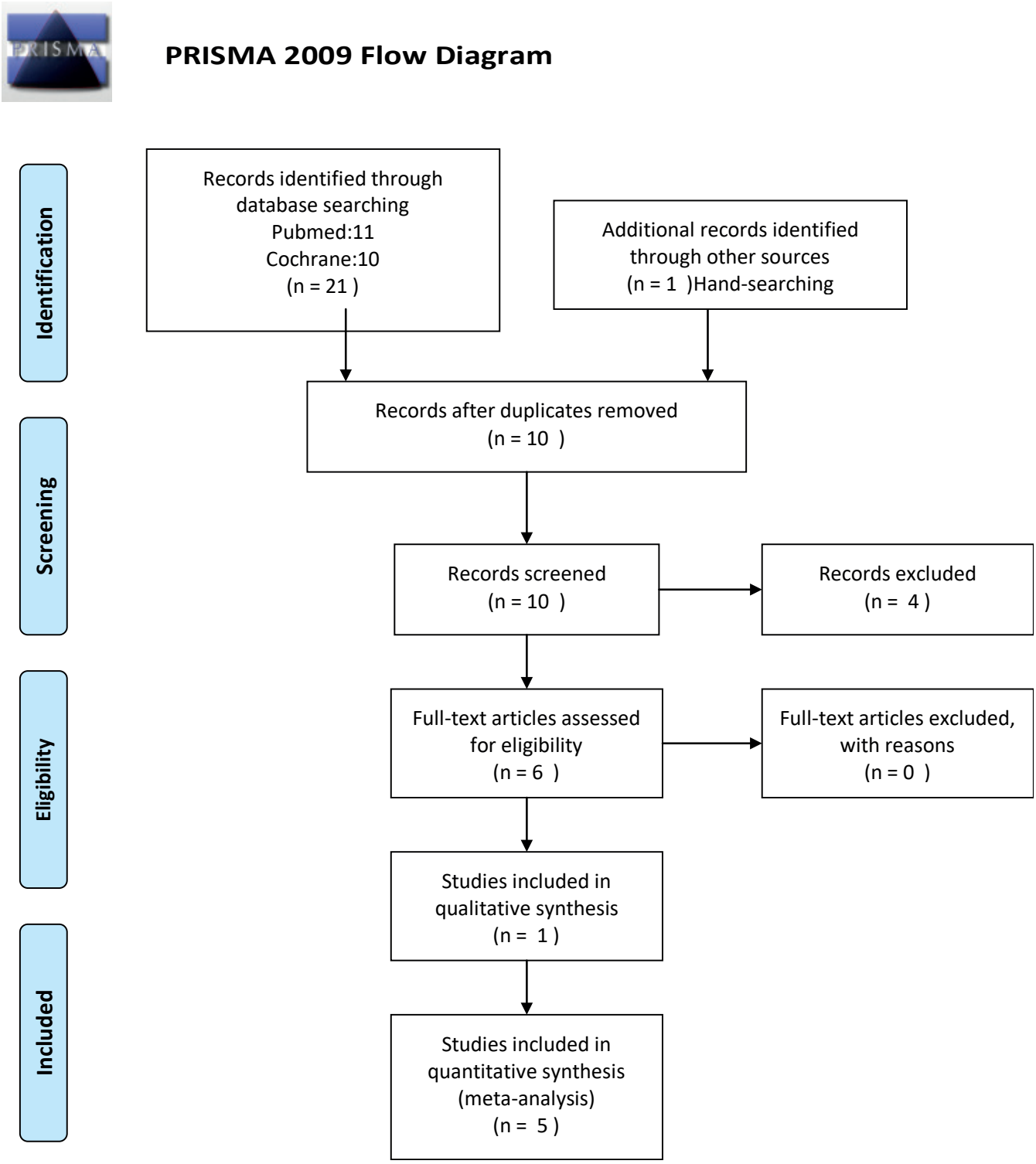


FIGURE 1: PRISMA FLOW DIAGRAM

searches of journals, conference abstracts and books and Contacting experts in the field were the other resources from which the studies were searched and considered."

"Data collection and analysis"

Selection of studies

The Rayyan online screening tool[11] was used for screening the search results independently by three review authors (RO, VS, PD) and articles were retrieved. The eligibility of each study were determined by briefing the abstracts of each study identified by the search. The studies that didn't clearly satisfy the inclusion criteria were eliminated by review authors. Full copies of all the remaining studies were obtained. The full texts of these studies were independently screened to select relevant studies by primary reviewers (RO, VS, PB).Any missing data or information in the studies which affected the study selection criteria then the respected authors were contacted either by telephone or email and the necessary clarification for the information were obtained. In situations of disagreement or dispute, a fourth author was asked for a judgment (PD). Anonymisation of the studies were not performed before assessment. Any language restrictions in the selection of studies was not considered as apart of limitation in executing this review. A "PRISMA flow chart" were 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"*[12]. Irrespective of the reporting of outcome data, studies were included in this review.

Data extraction and management

Three reviewers (RO, VS, PB) persuaded the data extraction done from "included studies" using a pre-defined data extraction form and was presented in "Characteristics of Studies Table"[13] (Table 1). Data were extracted in terms of type of study, details of participants, details of intervention, outcomes reported. Third reviewer (PD) resolved the discrepancy amongst the primary reviewers. The discrepancy "risk of bias assessment" resolved by fourth reviewer (MNK).

"Assessment of risk of bias in included studies

Risk of bias(RoB) were assessed independently by the three reviewers (RO, VS, PB) 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[12]. The discrepancy among the primary reviewers was resolved by fourth reviewer (MNK). We assessed 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"

Measures of treatment effect

Unit of analysis issues

Individual participant were 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[14]. Such trials were 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 executed an intention-to-treat analysis. Further information from the authors or manufacturers were asked if the published data were found to be incomplete, missing or inconsistent with RCT protocols. Authors were contacted by email if the included studies did not report 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"

The Chi2 test (P value 0.10 for statistical significance) was used to examine clinical heterogeneity, and the I2 statistic was utilised to quantify heterogeneity in the outcomes of the included studies. Significant heterogeneity[15] is defined as I2 over 75%; substantial heterogeneity is defined as I2 between 50% and 90%; moderate heterogeneity is defined as I2 between 30% and 60%; and mild heterogeneity is defined as I2 less than 40%. (12) If statistical heterogeneity with I2 more than or equal to 50% is found, relevant causes were investigated using predefined subgroup analysis, and a

random-effects model was used and reported.

Assessment of reporting biases

The studies included were 9 and hence funnel plot test for any asymmetry was not required.

Data synthesis

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.[14] If statistical heterogeneity showing I^2 greater than, or equal to 50% will be detected, then the sources of the heterogeneity was identified and the subsequent meta-analysis using a random-effects model was performed. Meta-analysis was performed using four studies. Data from all the four studies is tabulated in table no. 2 (Data Entry)

TABLE 2: DATA ENTRY

Parameters	Pradeep 2012		Pradeep 2013		Singhal 2017		Gupta 2019		Garg 2016		
Outcomes	Continious data		Continious data		Continious data		Continious data		Continious data		
	Mean of intervention±sd (ldd agents-smv+srp)	Mean of control ±sd (srp+placebo)	Mean of intervention±sd (ldd agent- aln+srp)	Mean of control ±sd (placebo+srp)	Mean of intervention±sd (ldd agent- ba+srp)	Mean of control ±sd (srp+placebo)	Mean of intervention±sd (ldd agent- zln+srp)	Mean of control ±sd (srp+placebo)	Mean of intervention±sd (ldd agents+srp))		Mean of control ±sd (placebo)
PI	Bl (n=37): 1.88±0.22 3 months(n=33): 0.97±0.18 6 months(n=33(:0.68+0.18	Bl(n=35): 1.90±0.20 3 months(n=33): 0.83±0.15 6 months(n=33): 0.66±0.18	Bl(n=35): 1.73 ±0.31 3 month(n=35):0.91 ± 0.27 6 months(n=30):0.20 ± 0.40	Bl(n=34):0.20 ±0.40 3 months(n=34):1.00 ± 0.28 6 months(n=30): 0.52 ± 0.24	BL(n=29):6.97 ±0.76 3 months(n= 25): 0.856±0.10 6 months(n= 25): 0.46±0.12	Bl(n=29):1.92±0.17 3 months(n=23): 1.23±0.15 6 months(n=23): 0.82±0.15	BL(n=20):2.30±0.25 3 months(n=19): 1.94±0.20 6 months(n=19): 1.64±0.17	Bl(n=20): 2.24±0.10 3 months(n=20): 1.86±0.06 6 months(n=20): 1.63±0.11	RSV+SRP	ATV	Bl(n=30): 1.85±0.32 3 months(n=30):0.99±0.26 6 month(n=30):0.84±0.28
GI	Bl: 2.83±0.27 3 months: 1.03±0.18 6 months:0.80±0.18	Bl:2.51±0.42 3 months:1.42±0.44 6 months:1.61±0.43	Bl: 2.54 ± 0.17 3 months: 1.01 ±0.41 6 months: 0.79 ±0.12	Bl:2.53 ±0.16 3 months: 1.15 ± 0.44 6 months: 0.88 ± 0.29	Bl:2.56±0.28 3 months: 0.41±0.12 6 months: 0.39±0.14	Bl:2.53±0.26 3 months: 1.44±0.18 6 months:0.73±0.21	Bl:2.32±0.24 3 months: 1.90±0.14 6 months: 1.62±0.16	Bl: 2.29±0.13 3 months: 1.89±0.10 6 months: 1.63±0.11	Baseline:2.34±0.59 3 months:1.01±0.29 6 months:0.70±0.17	Baseline:2.29±0.55 3 months:1.07±0.32 6 months:0.80±0.28	Baseline:2.25±0.58 3 months:1.37±0.36 6 months:1.20±0.32
									BL(n=30):1.87±0.34 3 months(n=30): 0.97±0.25 6 months(n=30):0.74±0.23	Bl(n=30):1.83±0.30 3 months(n=30):0.96±0.25 6 months(n=30):0.73±0.21	

Parameters	Pradeep 2012		Pradeep 2013		Singhal 2017		Gupta 2019		Garg 2016		
Outcomes	Continious data		Continious data		Continious data		Continious data		Continious data		
RVCAL	Bl: 7.92±1.50 3 month: 4.22±1.31 6 month:3.28± 1.40	Bl: 7.43±1.53 3 month:5.07±0.99 6 month: 4.97± 0.89	Bl:7.30 ±0.79 3 months: 5.07 ± 0.64 6 months: 4.07 ±0.64	Bl:7.27 ±0.78 3 months: 6.33 ± 0.66 6 months: 6.03 ±0.76	Bl: 8.20±1.35 3 months: 6.16±1.31 6 months: 5.28±1.59	Bl:7.91±1.34 3 months: 6.95±1.36 6 months: 6.39±1.19			Bl:8.56±1.22 3 months:5.90±1.24 6 months:4.93±1.25	Bl:8.83±1.11 3 months:6.56±1.10 6 months:5.83±1.36	Bl:8.86±1.07 3 months:7.56±1.04 6 months:7.06±0.86
Rhcal	Bl:8.43±1.28 3 month: 4.93±0.94 6 month: 4.10± 1.19	Bl: 7.86± 1.46 3 month: 5.56±1.27 6 month: 5.43± 1.15	Bl:8.07 ± 0.64 3 months: 6.10 ±0.66 6 months: 5.03 ± 0.56	Bl:8.03 ±0.81 3 months: 7.17 ± 0.79 6 months: 6.97 ± 0.76	Bl: 8.32±1.14 3 months: 6.48±1.38 6 months: 5.64±1.07	Bl: 8.47±1.37 3 months: 7.43±1.30 6 months: 6.34±1.19			Bl:8.26±1.04 3 months:5.96±1.47 6 months:5.03±1.32	Bl:8.43 ±1.13 3 months:6.43±1.25 6 months:5.73±1.25	Bl:8.36±0.99 3 months:7.06±1.20 6 months:6.50±1.30

Subgroup analysis and investigation of heterogeneity: We took the subgroups on the basis of type and duration of the intervention given.

RESULTS

INCLUDED STUDIES

A total of six studies were identified based on the inclusion and exclusion criteria's. The details of the studies are given in Table 1[16–20]. Only articles published in English were included.

TABLE 1: Summary of included articles

Articles	Singhal 2017	Pradeep 2013	Garg 2016	Gupta et al	Pradeep 2012
Country	Bangalore, India	Bangalore, India	Bangalore, India	Lucknow, India	Bangalore, India
Type of study	RCT	RCT	RCT	RCT	RCT
Details of group					
Number of group	IG:(SRP+LDD),CG: (SRP+PLACEBO)	IG:(SRP+ALN),CG: (SRP+Placebo)	CG:(SRP+placebo), IG1 (SRP+RSV),IG2: (SRP+ATV)	IG:20(SRP+ZLN), CG:20 (SRP+PLACEBO)	IG:36(SRP+SMV), CG:36(SRP+PLACEBO)
Number of Patients	64 subjects	69 subjects	105 subjects	40 subjects	72 subjects
Number of males and females in the group	34males/30females	37males/32females	55 males, 60 females	IG:20 (8 females, 12males) CG:20(9 females, 11males)	38 males, 32 females
Number of patients completed study	48 subjects	57 subjects	90 subjects	39 subjects	66 subjects
Participation details					
Age	30-50 years	30-50 years	NR	30-50years	30-50 years
Type of periodontal disease	Chronic Periodontitis	Chronic Periodontitis	Chronic periodontitis	Chronic periodontitis	Chronic periodontitis

Articles	Singhal 2017	Pradeep 2013	Garg 2016	Gupta et al	Pradeep 2012
Country	Bangalore, India	Bangalore, India	Bangalore, India	Lucknow, India	Bangalore, India
Type of study	RCT	RCT	RCT	RCT	RCT
Furcation involvement	Present	Present	Present	Absent	Present
Type of tooth Involved	Asymptomatic, vital mandibular first molar	Asymptomatic, vital mandibular first molar	Mandibular molars	NR	Asymptomatic mandibular first and second molars
Grade of furcation defect	Buccal Class II	Buccal class II	Buccal class II	NR	Buccal class II
Tooth mobility	Absent	Absent	Present	NR	ABSENT
Intervention					
Type	SRP+0.1ml of 0.75% BA gel+OHI	SRP+1%ALN gel+OHI	SRP+RSV/ATV+OHI	SRP+ZLN+OHI	SRP+SMV+OHI
Number of sites	one site per patient	one site per patient	furcation areas , respective sites -NR	sites where periodontal pockets present following SRP after 1 month	furcation areas , respective sites -NR
Duration	one year	one year	9 months	6 months	6 months
Frequency	baseline, 3months, 6months.	baseline, 3months, 6months, 12months	baseline, 6 months , 9 months	baseline, 3 months , 6 months	baseline, 3 months , 6 months
Adverse Reaction	No	No	NR	NR	NO
Antibiotics/ Antiinflammtory prescribed after treatment	yes	No	No	NR	NO
Outcomes					
Name	primary- PPD,PI,GI,RVCAL, RHCAL	primary- PPD,PI,GI,RVCAL, RHCAL	Primary:PPD ,PI,GI,RVCAL,RHCAL	Primary:PPD ,PI,GI,RVCAL,RHCAL	Primary:PPD ,PI,GI,RVCAL,RHCAL
	secondary- Bone defect depth, Bone defect fill.	secondary- Bone defect depth, Bone defect fill.	secondary- Bone defect depth, Bone defect fill.	secondary- Bone defect depth, Bone defect fill.	secondary- Bone defect depth, Bone defect fill.
Technique/Definition	PPD≥ 5mm	PPD≥ 5mm	PPD≥ 5mm	PPD≥5mm, CAL≥4mm,	PPD≥ 5mm
	Horizontal probing≥ 3mm following SRP	Horizontal probing ≥ 3mm following SRP	Horizontal probing ≥ 3mm following SRP	vertical bone loss>3mm	Horizontal probing ≥3mm following SRP
Instrument used	A custom made acrylic for RVCAL and RHCAL	A custom made acrylic for RVCAL and RHCAL	A custom made acrylic for RVCAL and RHCAL	A custom made acrylic for RVCAL and RHCAL	A custom made acrylic for RVCAL and RHCAL
	Color-coded periodontal probe (PCP-UNC-15probe	Color-coded periodontal probe for vertical measurement	Color-coded periodontal probe (PCP-UNC-15probe	Color-coded periodontal probe (PCP-UNC-15probe	Color-coded periodontal probe (PCP-UNC-15probe
	HU-Friedy, Chicago IL, USA for vertical measurement)	Furcation probe for horizontal measurement			
	Nabers furcation probe				
	Hu-Friedy, USA for horizontal measurement				
Time of reporting	6 months	12 months	6 months	6 months	6 months

Forest Plots

The analysis of relative vertical clinical attachment loss (RVCAL), and relative horizontal clinical attachment loss (RHCAL) was done separately for the interventional (SRP plus LDD) and control groups (SRP plus placebo). The

details of the studies included for meta- analysis are given in figure 3-6. All studies reporting the adjunctive use of LDD agents such as Simvastatin, Atorvastatin, Boric acid, Alendronate, and Zolendronate were included. Studies reporting the use of phytopharmaceuticals either alone or in combination with allopathic medications were excluded. Five studies were found to be eligible. The conclusion regarding the overall effect size estimates were made based on the meta-analysis.

Plaque index

All the included studies reported PI at baseline and after 6 months (Pradeep 2012 , Pradeep 2013 , Garg 2016 , Singhal 2017 , Gupta 2019). All the studies included in this comparison used different drugs for local application. Three studies that used allendronate (Pradeep 2013), atorvastatin (Garg 2016) and boric acid (Singhal 2017) as local drugs found better PI with SRP+LDD verses SRP+Placebo (Pradeep 2013,Garg 2016, Singhal 2017) and two studies that used simvastatin (Pradeep 2012) and zolendronate (Gupta 2019) as local drugs did not show any beneficial effect of SRP+LDD. The overall meta-analysis showed marginally significant reduction in plaque scores six months after SDD+LDD (MD -0.15; 95% CI -0.32 to 0.02; P <0.00001; I^2 94%; five studies; 273 participants). However; in view of significant heterogeneity (I2=94%), the results needs to be interpreted with caution as shown in figure 3[17,19–22].

Gingival Index

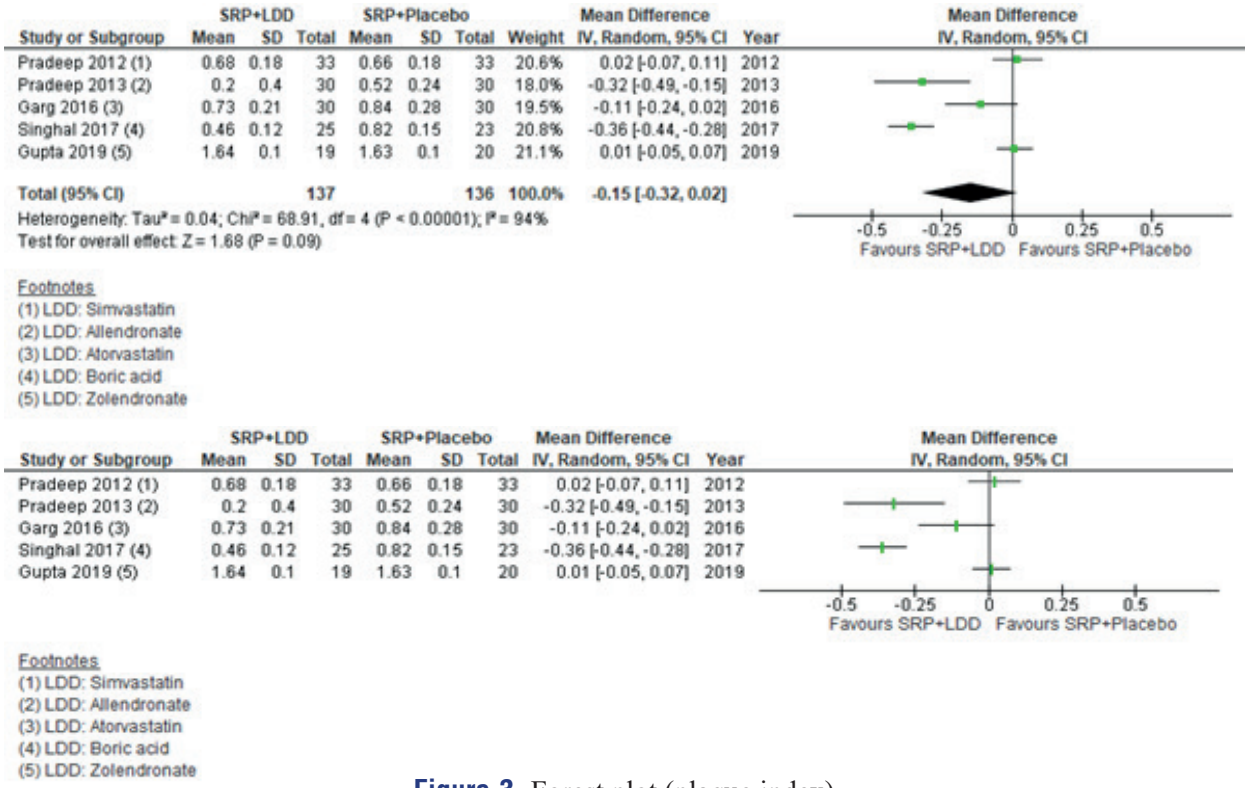
All four included studies (Pradeep 2012 , Pradeep 2013 , Singhal 2017 , Gupta 2019)[17,19–21,21,22]compared the gingival index in the interventional group and control group at baseline and after 6 months. All the studies included in this comparison used different drugs for local application. The three studies that used Simvastatin(Pradeep 2012), Allendronate(Pradeep 2013) and Boric acid(Singhal 2017) as local drug found better GI with SRP+LDD versus SRP+Pacebo (Pradeep 2012 , Pradeep 2013 , Singhal 2017).However in one of the included study (Gupta 2019) that used Zolendronate as the local drug no significant improvement in the GI was found. Three studies that used Simvastatin(Pradeep 2012), allendronate (Pradeep 2013), and boric acid (Singhal 2017) as local drugs found better GI with SRP+LDD verses SRP+Placebo (Pradeep 2013,Pradeep2012, Singhal 2017) and one study that used Boric acid(Singhal 2017) as local drugs did not show any beneficial effect of SRP+LDD. The overall meta-analysis showed marginally significant reduction in gingival scores six months after SDD+LDD (MD -1.17 ; 95% CI -2.29 to -0.05; P <0.00001 ; four studies;107 participants). However; in view of significant heterogeneity (I2=93%), the results needs to be interpreted with caution as shown in figure 4[17,19–21].

Relative Vertical Clinical Attachment Loss (Rvcal)

All the included studies reported RVCAL at baseline and after 6 months (Pradeep 2012 , Pradeep 2013 , Garg 2016 , Singhal 2017). All the studies included in this comparison used different drugs for local application. All four studies that used Atorvastatin (Pradeep 2012),Allendronate (Pradeep 2013), Atorvastatin (Garg 2016) and Boric acid (Singhal 2017) as local drugs found equally favourable in improving of RVCAL with SRP+LDD verses SRP+Placebo (Pradeep2012, Pradeep 2013,Garg 2016, Singhal 2017) .The overall meta-analysis showed marginally significant increase in relative vertical attachment level six months after SDD+LDD (MD -1.57 ; 95% CI - 1.98t o -1.16; P <0.00001; four studies; 118 participants).However the percentage of variation (I^2 – 55%) was found to be minimum in all the four included studies, therefore making the interpretation of result favourable as shown in figure 5. [17,20–22]

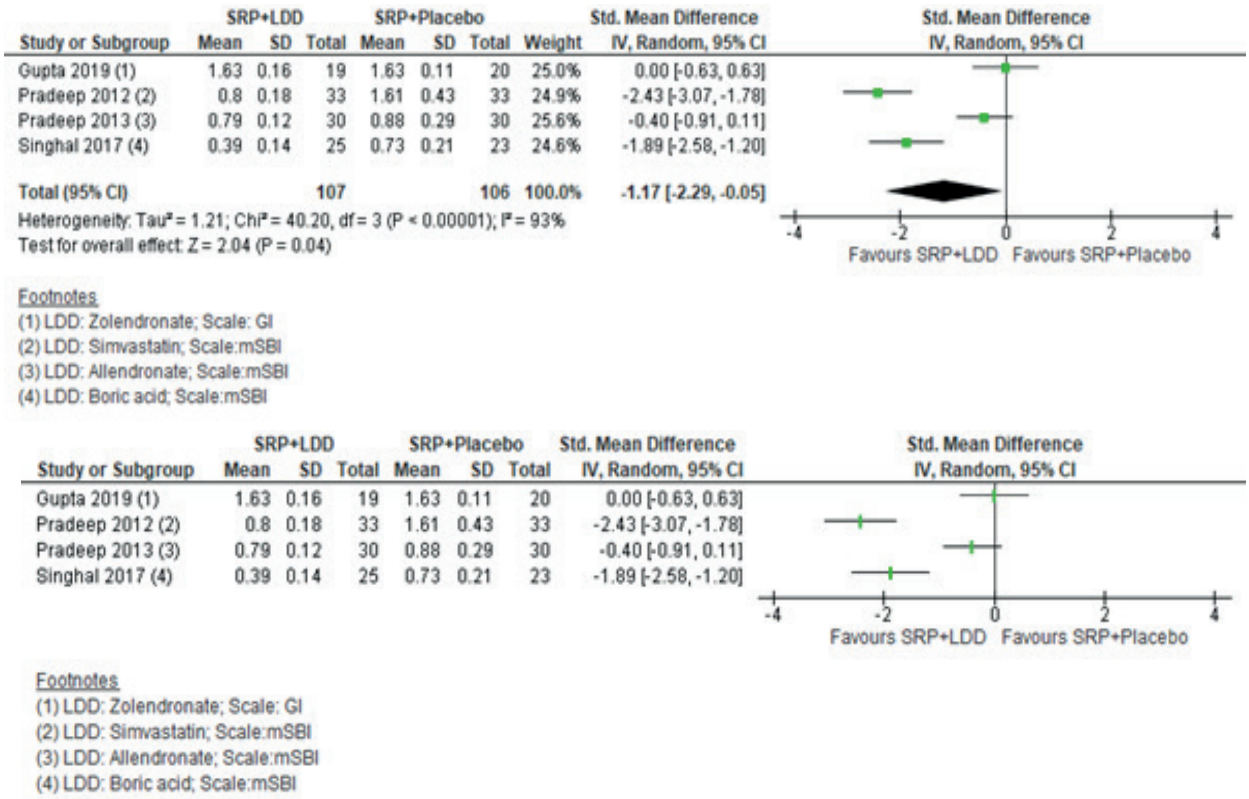
Relative Horizontal Clinical Attachment Loss (Rhcal)

All the included studies reported RHCAL at baseline and after 6 months (Pradeep 2012 , Pradeep 2013 , Garg 2016 , Singhal 2017). All the studies included in this comparison used different drugs for local application. All four studies that used Atorvastatin (Pradeep 2012),Allendronate (Pradeep 2013),Atorvastatin (Garg 2016) and Boric acid (Singhal 2017) as local drugs found equally favourable in improving of RHCAL with SRP+LDD verses SRP+Placebo (Pradeep2012, Pradeep 2013,Garg 2016, Singhal 2017) .The overall meta-analysis showed marginally significant increase in relative horizontal attachment level six months after SDD+LDD (MD - 1.22; 95% CI -1.87 to -0.58) ; P =0.0005; four studies ;118 participants) However inspite of insignificant improvement in the relative horizontal attachment level in the SRP+LDD versus SRP+Placebo(Pradeep2012, Pradeep 2013,Garg 2016, Singhal 2017); in view of significant heterogeneity found between all four studies (Pradeep2012, Pradeep 2013,Garg 2016, Singhal 2017) (I2=83%), the results needs to be interpreted with caution as shown in figure 6[17,20–22].



SRP+LDD
SRP+Placebo
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total IV, Random, 95% CI Year
IV, Random, 95% CI
Pradeep 2012 (1) 0.68 0.18 33 0.66 0.18 33 0.02 [-0.07, 0.11] 2012
Pradeep 2013 (2) 0.2 0.4 30 0.52 0.24 30 -0.32 [-0.49, -0.15] 2013
Garg 2016 (3) 0.73 0.21 30 0.84 0.28 30 -0.11 [-0.24, 0.02] 2016
Singhal 2017 (4) 0.46 0.12 25 0.82 0.15 23 -0.36 [-0.44, -0.28] 2017
Gupta 2019 (5) 1.64 0.1 19 1.63 0.1 20 0.01 [-0.05, 0.07] 2019
-0.5 -0.25 0 0.25 0.5
Favours SRP+LDD Favours SRP+Placebo
Footnotes
(1) LDD: Simvastatin
(2) LDD: Allendronate
(3) LDD: Atorvastatin
(4) LDD: Boric acid
(5) LDD: Zolendronate

Figure 3. Forest plot (plaque index)



SRP+LDD
SRP+Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total IV, Random, 95% CI
IV, Random, 95% CI
Gupta 2019 (1) 1.63 0.16 19 1.63 0.11 20 0.00 [-0.63, 0.63]
Pradeep 2012 (2) 0.8 0.18 33 1.61 0.43 33 -2.43 [-3.07, -1.78]
Pradeep 2013 (3) 0.79 0.12 30 0.88 0.29 30 -0.40 [-0.91, 0.11]
Singhal 2017 (4) 0.39 0.14 25 0.73 0.21 23 -1.89 [-2.58, -1.20]
-4 -2 0 2 4
Favours SRP+LDD Favours SRP+Placebo
Footnotes
(1) LDD: Zolendronate; Scale: GI
(2) LDD: Simvastatin; Scale:mSBI
(3) LDD: Allendronate; Scale:mSBI
(4) LDD: Boric acid; Scale:mSBI

Figure 4. Forest plot (gingival index)

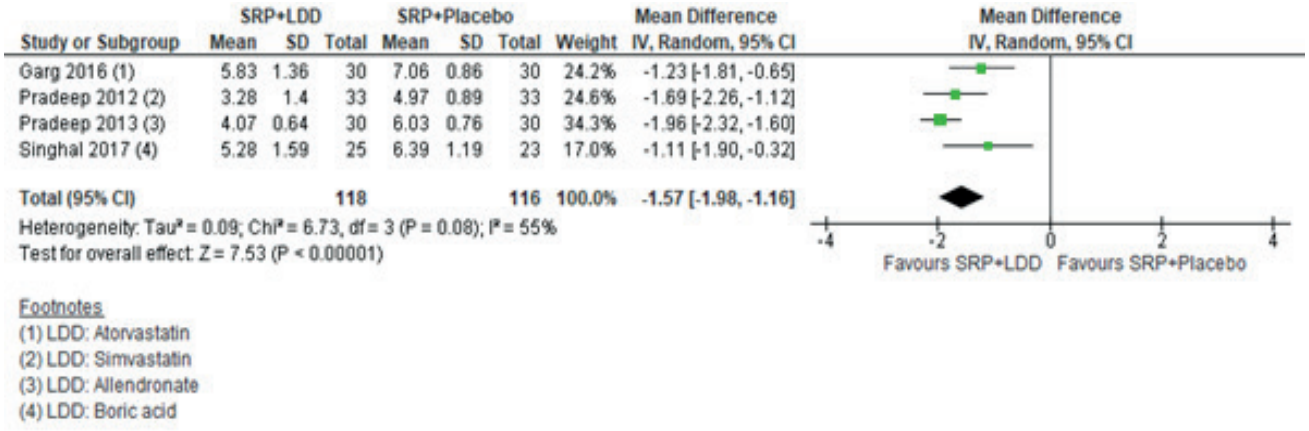


Figure 5. Forest plot relative vertical clinical attachment loss (rvcal)

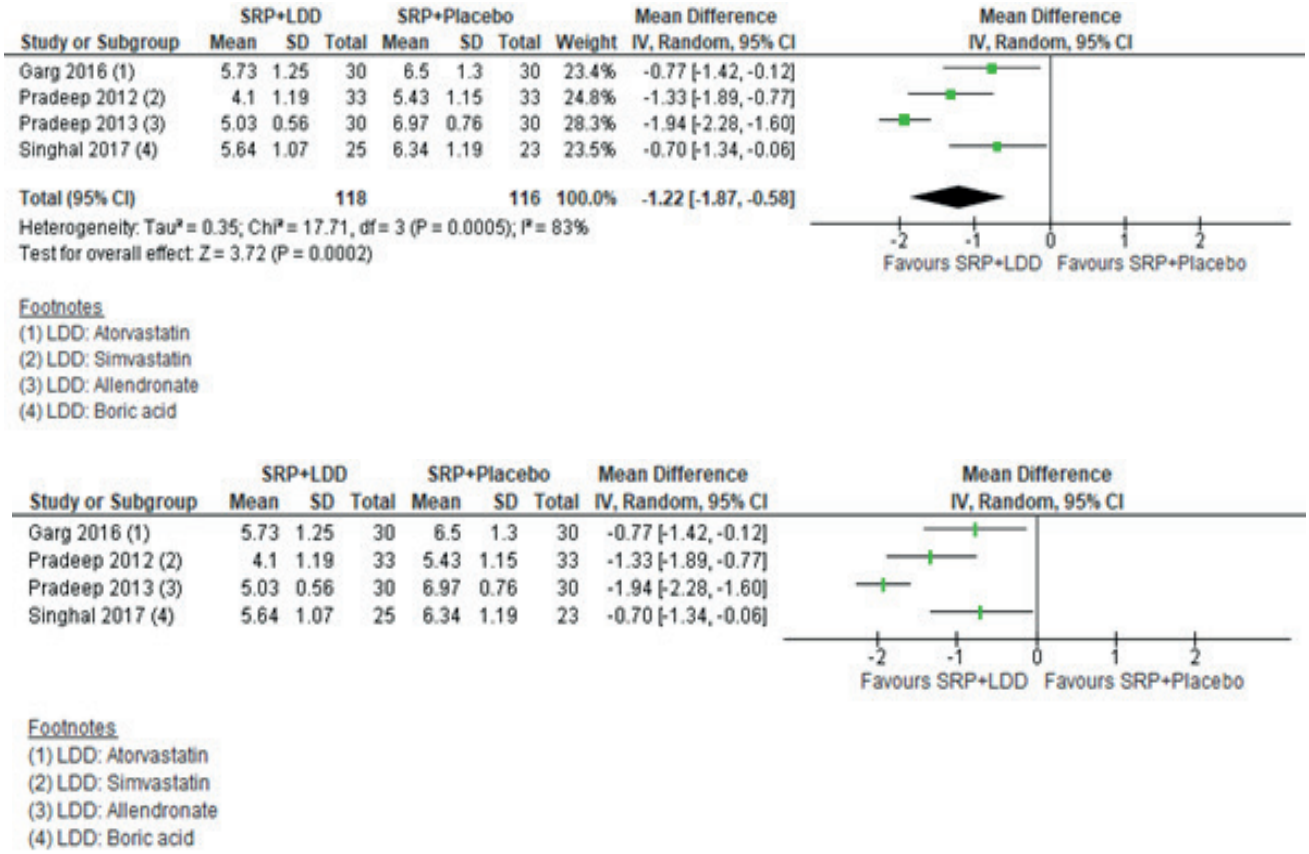


Figure 6. Relative horizontal clinical attachment loss (rhcal)

DISCUSSION

Study participants

The details of the participant recruitment are given in Table 1[16–20]. All the studies including participants with chronic periodontitis having furcation defect were considered. Age of the participants ranged from 30-50 years.

Intervention

The included studies measured changes in the clinical periodontal parameters after application of LDD agents as an adjunct to SRP at baseline, 3 months, and 6

months[16–20]. All the studies randomly divided patients into two groups. Interventional group received LDD agent as an adjunct to SRP and control group received SRP plus placebo. However,LDD agent varied in all the studies. Study by Pradeep et al used Simvastatin and Alendronate as LDD agents [17,20]. Singhal et al , Garg et al , and Gupta et al used boric acid, Atorvastatin and Zolendronate, respectively[18,19,21]. However,the study by Garg et al included three groups, one that received SRP plus Rouvustatin , group 2 received SRP plus Atorvastatin and group 3 received SRP plus placebo[22].

Comparison

All the studies included two groups and only one LDD agent except for Garg et al. Garg et al included three groups, group1 received SRP plus Rouvustatin, group 2 received SRP plus Atorvastatin and group 3 received SRP plus placebo[22]. All the studies measured clinical periodontal parameters at baseline, 3 months and 6 months except for Pradeep et al 2013, where a follow-up period of 12 months was considered[17].

Primary outcome

All the included trials reported data on plaque index (PI), gingival index (GI), relative vertical clinical attachment loss (RVCAL), relative horizontal clinical attachment loss (RHCAL)[17,19–22]. Concomitantly, Gupta et al reported data on tooth specific clinical attachment loss (TsCAL)[19].

Secondary outcome

All the included studies reported data on bone defect depth [17,19–22]. In addition, Gupta et al also considered other parameters such as bone defect angle, radiographic angle fill, and volumetric defect gain[19]. Pradeep et al also measured the percentage bone fill[17,20].

Excluded studies

The study by Gautami 2012 was excluded since it was a case report[23]. The studies by Tonnetti et al and Takeuchi et al were not randomized controlled trials and hence were excluded[24,25]. Two studies included unpublished data and therefore, were excluded[26,27].

Risk of bias in included studies

All the studies were evaluated for risk of bias. Various types of associated bias are tabulated in table 3 (Risk of bias table). All studies were at low risk bias study. Risk of bias in other domains was unclear or low. Risk of bias is shown in the figure2

Table 3: Risk of bias

Phase	Pradeep 2012	Comment	Pradeep 2013	Comment	Singhal 2017	Comment	Gupta 2019	Comment	Garg 2016	Comment
	RoB		RoB		RoB		RoB		RoB	
Random sequence generation (selection bias)	LOW RISK	Quote: "36 participants were randomly assigned by computer generated system."	LOW RISK	"After patient enrollment by an examiner (ARP),sites were randomly assigned (by a computer-generated system)"	LOW RISK	"The patients were enrolled by the examiner (A.R.P), and sites were then randomly assigned (by a computer-generated system)"	LOW RISK	"After enrollment, the patients were randomly assigned (by a computer-generated system using Excel 2013 v 15.0 for Microsoft windows) either to the ZLN group (n = 20; 8 females and 12 males; 1 dropout that failed to undergo reevaluation after 6 months) or control group (CG) (n = 20; 9 females and 11 males)."	LOW RISK	"The randomization process was made externally by the statistical unit using a computer generated random table, and investigators were neither involved in the randomization process nor aware of the assigned group in all outcome evaluations."

Phase	Pradeep 2012	Comment	Pradeep 2013	Comment	Singhal 2017	Comment	Gupta 2019	Comment	Garg 2016	Comment
	RoB		RoB		RoB		RoB		RoB	
Allocation concealment (selection bias)	UNCLEAR	Not reported	UNCLEAR	Not reported	UNCLEAR	Not reported	LOW RISK	"Patients as well as the investigator "A" performing SRP both were masked for allocation into the ZLN or placebo group"	LOW RISK	"investigators were neither involved in the randomization process nor aware of the assigned group in all outcome evaluations."
Blinding of participants and personnel (performance bias)	UNCLEAR	NR	UNCLEAR		LOW RISK	"SRP local delivery of .75% BA gel or placebo gel in the BA group and placebo groups was done by the same operator (S.S) who was blinded to the treatment groups. The BA and control sites were not revealed to the patients."	LOW RISK		LOW RISK	investigators were neither involved in the randomization process nor aware of the assigned group in all outcome evaluations.
Blinding of outcome assessment (detection bias)	UNCLEAR	Not reported	UNCLEAR	Not reported	UNCLEAR	Not reported	LOW RISK	"TSPPD and TSCAL were measured to the nearest millimeter with the help of a UNC 15 periodontal probe (Hu-Friedy Mfg.Co., LLC, Chicago, United States) by another investigator "B" (masked to the treatment received) interproximally in all the chosen sites."	LOW RISK	"investigators were neither involved in the randomization process nor aware of the assigned group in all outcome evaluations."
Incomplete outcome data addressed (attrition bias)	LOW RISK	lost to follow up: Ig:2, Cg:4	LOW RISK	lost to follow up: Ig:1, Cg:2	LOW RISK	lost to follow up: Ig:4, Cg:6	LOW RISK	lost to follow up: Ig:0, Cg:0	LOW RISK	lost to follow up: Ig:0, Cg:0
Selective reporting (reporting bias)	LOW RISK		LOW RISK		LOW RISK		LOW RISK		LOW RISK	

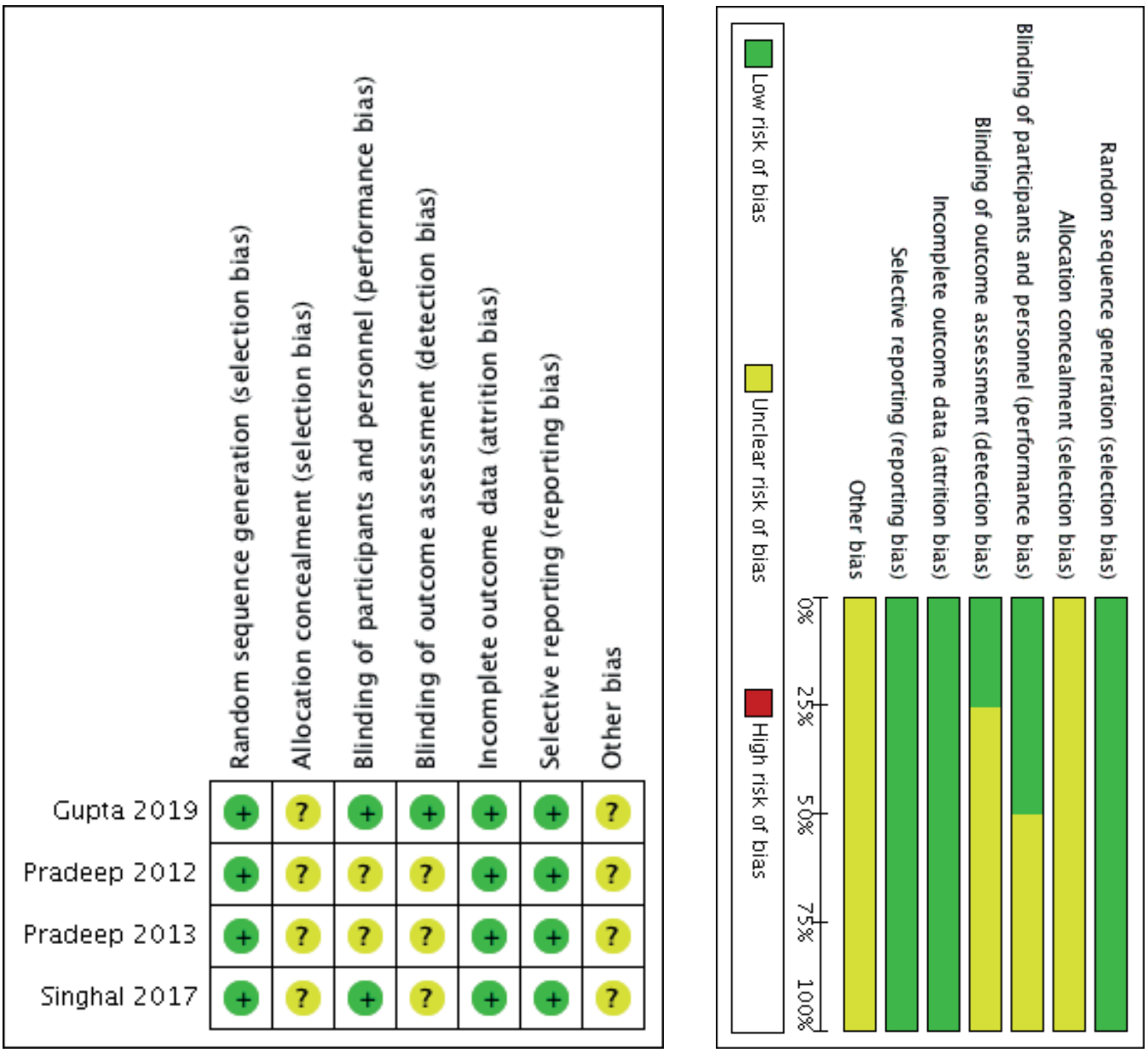


Figure2. Risk of bias of the included studies.

Allocation (selection bias)

Random sequence generation: All studies were at low risk of selection bias for random sequence generation. All the studies randomized the participants using a computer-generated system using Excel 2013 v 15.0 for Microsoft windows. Strasser 2008 mentioned that a random allocation sequence was produced.

Allocation concealment: Gupta 2019 stated that "Patients as well as the investigator "A" performing SRP both were masked for allocation, into the ZLN or placebo group" that is clearly low risk. Garg 2016 stated that "investigators were neither involved in the randomization process nor aware of the assigned group in all outcome evaluations.", hence we judged it as low risk. Details of allocation of rest of the studies were not mentioned clearly and it was judged as unclear.

Blinding (performance bias and detection bias) : All the included studies were double-blind. However, since the type of blinding was not specified in two studies they were categorized to be unclear.

Incomplete outcome data (attrition bias) : The included studies reported low attrition bias.

Selective reporting (reporting bias) : Pradeep 2012, Pradeep 2013, Gupta 2019, Singhal 2017, Garg 2016 have their protocols registered in clinical trial registry, and are in low risk of bias.

Other potential sources of bias: No other potential sources of bias in the included studies.

Overall completeness and applicability of evidence: The effectiveness of adjunctive use of LDD agents with SRP was explored in chronic periodontitis subjects with furcation involvement. Six out of total nine studies (Table 1) were included for meta-analysis. Evidence from these included studies was good with low bias.

Quality of the evidence: Based on the quality of methodology used and reporting of adequate data the quality of evidence for all our primary outcomes was considered to be moderate. These conclusions should considered with caution as the smaller sample size in all included studies and the shorter follow-ups limited us to draw a reasonable conclusion. On the basis of "Summary of findings table" and the forest plots it can be concluded that the LDD agents used as an adjunct to SRP are more effective in the treatment of furcation defects compared to SRP alone.

CONCLUSION

We included five studies reporting data from 390 participants, aged 18+ years, comparing Local drug delivery agents plus scaling and root planing with scaling and root planing with placebo. Studies reported data on periodontal parameters like pocket depth, gingival bleeding, clinical attatchment loss. Indices including plaque index and gingival index. Ipshita2018 used and compared both allopathic and herbal agent hence was not included for meta-analysis. Due to the differences in the time of reporting of the included studies, all of them were not included for meta-analysis. Meta-analysis was done including five studies(Pradeep2012, Pradeep 2013, Gupta2019, Singhal2017, Garg2016,) It supported that local drug delivery as an adjunct to scaling and root planing is more effective than scaling and root planing alone.

Compliance with Ethical Standards:

- Conflict of Interest: None
- Funding: None
- Ethical approval: Not required
- Informed Consent: Not required

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