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Clinical Efficacy of Papilla Preservation Flaps with Regenerative Biomaterials in the Treatment of Periodontal Intrabony Defects – A Systematic Review and Meta-Analysis

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Abstract
Aim: *This paper is a systematic review and meta-analysis of randomized controlled trials to evaluate the clinical efficacy of papilla preservation flaps with the regenerative biomaterials in the treatment of periodontal intrabony defects.*
Materials and Methods: *A meta-analysis was conducted to evaluate the clinical efficacy of papilla preservation flaps with the regenerative biomaterials in the treatment of intrabony defects with a search for articles in the PUBMED search site. Study outcomes were reported through evidence tables and a quantitative synthesis through a meta-analysis by using OpenMEE®.*
Results: *Seventeen studies were identified and considered in the literature search for inclusion in the meta-analysis. Among 225 periodontal intrabony defects evaluated at 6 months, 112 were treated randomly by papilla preservation flaps with the regenerative biomaterial and 113 were treated using papilla preservation flaps alone. There was substantial heterogeneity across the studies in reporting the outcomes of PPD reduction ($p<0.001$) and moderate heterogeneity in reporting the outcome of CAL gain ($p=0.085$). Pooled estimates showed that regenerative material used in combination with papilla preservation flaps showed more PPD reduction ($p=0.002$) and CAL gain ($p<0.001$) than the use of papilla preservation flaps alone.*
Conclusion: *The results of our meta-analysis seem to indicate that on a short-term follow-up, the use of papilla preservation flaps combined with regenerative biomaterials have better clinical outcomes in terms of PPD reduction and CAL gain compared with papilla preservation flaps alone.*
Key words: *Regenerative therapy, Papilla preservation flaps, Flap surgery*

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I. Introduction

Primary closure of the bony defect is the essential component for obtaining a favorable outcome in periodontal regeneration. Lack of primary closure contributes to loss of surgical clot, delayed healing and unpredictable graft outcomes. For complete coverage of the regenerative material placed in the osseous defect, the flap was designed for minimal soft tissue injury [1-4]. A surgical approach that tears the papilla leads to shrinkage and reduction in the height of interdental papilla leading to exposure of the interproximal embrasures which is unaesthetic in appearance.

There are different surgical approaches available to obtain primary closure of the flap that preserve interdental tissue and improve esthetics: Conventional Papilla preservation flap[1], Modified papilla preservationflap[2], Simplified papilla preservation flap[3], Whale's tail technique[4], Minimally Invasive Surgical Technique(MIST)[5], Modified Minimally Invasive Surgical Technique(M-MIST)[6], Single Flap approach[7], Entire Papilla Preservation Technique[8], Non-Incised Papillae Surgical Approach(NIPSA)[9].

Since the publication of these approaches, several articles have been devoted to flap designs and surgical procedures to maintain full papillary form and soft tissue preservation during surgical access. These procedures have also been shown to have positive clinical outcomes like pocket probing depth (PPD) reduction and clinical attachment level (CAL) gain when treating interdental intrabony defects with or without the additional use of regenerative materials [12],[13].

In systematic reviews and meta-analysis by Murphy and Gunsolley[14] and Needleman[15], intrabony

defects that were treated with regenerative biomaterial revealed a significant CAL gain, PPD reduction and REC coverage than flap alone. In another systematic review, Trombelli found considerable CAL and PPD changes and increased defect fill with regenerative biomaterial like GTR when compared with flap alone[16]. These reviews focused on the significance of the use of biomaterials but also emphasized the inconsistency among studies and the obscurity in evaluating the clinical relevance of the findings.

Various surgical approaches have advanced from large flaps to minimal ones in an attempt to preserve the soft tissues as much as possible[17],[18]. Recently, Aslan introduced the entire papilla preservation flap (EPP) technique that maintains the whole interdental papilla in deep and wide intrabony defects[8]. Incision design aims to limit the flap mobility to facilitate blood clot stabilization minimizing invasiveness. Earlier these concepts were advanced by Harrel and Rees[19] and later Cortellini introduced the Minimally Invasive Surgical Technique (MIST)[5] and its modification, the Modified Minimally Invasive Surgical Technique (M-MIST)[6] and Trombelli has given the single flap approach (SFA)[7]. Traditionally, the regeneration of periodontal tissue has always been limited by the anatomic defect. Surgical techniques (such as soft tissue wall technique[17]) has been introduced, to overcome these limitations. Recently, Rodriguez proposed a new surgical technique i.e the Non-Incised Papillae Surgical Approach [10] to treat deep intraosseous defects using an apical approach. The surgical procedure and regenerative biomaterials are utilized to strengthen the soft tissues for clot stabilization and to avoid a collapse into the defect [11].

This paper is a systematic review and meta-analysis of randomized controlled trials to evaluate the clinical efficacy of papilla preservation flaps with regenerative biomaterials in the treatment of intrabony defects.

II. Material And Methods

Literature search

A meta-analysis was conducted to evaluate the clinical efficacy of papilla preservation flaps with regenerative biomaterials in the treatment of intrabony defects with a search for articles in the PUBMED search site. In this, a single reviewer selected English language articles published from January2001 to June 2019, using the keywords "papilla preservation flaps", "single buccal flap approach" and "periodontics", "minimally invasive surgery" and "periodontics", "microsurgical access flap" and "periodontics", "randomized controlled trials of intrabony defects" and "periodontics".

The studies were included based on the following criteria: English language, randomized clinical trials (RCT) of papilla preservation flaps with and without regenerative material, studies with a mean follow-up period between 6 and 24 months and defect sites with pocket depth (PD) ≥5mm. The exclusion criteria were studies based on questionnaire or interview, purely radiographic or histologic studies or studies based on papilla preservation techniques in implants.

Data extraction and analysis

The titles identified by the search were screened. The abstracts of all studies of possible relevance were obtained and screened. When studies met the inclusion criteria or when insufficient data from abstracts were available to evaluate inclusion criteria, the full-text article was obtained. The selected papers were screened independently by the reviewers to confirm whether they met the inclusion criteria or not. The outcome measures were probing pocket depth (PPD) reduction and clinical attachment level (CAL) gain.

Meta-Analysis

Study outcomes were reported through evidence tables and a quantitative synthesis through a meta-analysis. For data analysis, OpenMEE® (Open-source software for meta-analysis, Brown School of Public Health, Rhode Island, USA) was used. Mean and SD were preferred for expressing the results of continuous outcomes. Heterogeneity was evaluated through Cochrane's test (I^2 test) on the level of $\alpha = 0.10$. If the heterogeneity was considerable (I^2>50%), the random-effects model or subgroup analysis was employed; if the heterogeneity was non-significant, the fixed model was adopted.

III. Results

Seventeen[20-36] studies were considered and identified in the literature search for inclusion in the meta-analysis *(Figure 1)*. The characteristics of these 17 RCTs are summarized in Table 1. Among these studies, Cortellini et al. contained three groups (one with surgery alone, one with surgery combined with EMD or EMD plus bone grafts). For the meta-analysis, only the surgery combined with EMD and surgery alone were included. Stein et al. had three groups, which are, one with surgery alone, one with surgery with biphasic calcium phosphate (BCC) and one with autogenous bone spongiosa (ABS). For the meta-analysis, only the surgery with BCC and surgery alone were included.

The clinical outcomes at six and twelve months were reported in two studies, so the results for both

follow-ups were used in the meta-analysis. Because the length of follow-up might affect the clinical outcomes of patients, the results were pooled at 6-months [23],[29],[31-33],[35] together as the 6M group, and the results at 12-months [20-28],[30],[31],[34],[36] together as the 12M group. The primary clinical outcomes of the present meta-analysis were probing pocket depth (PPD) reduction and gain of CAL.

***6M group*:** There were 225 periodontal intrabony defects in this group. Among these defects, 112 were treated randomly by papilla preservation flaps with the regenerative biomaterial and 113 were treated using papilla preservation flaps alone. In all six studies, the outcomes of PPD reduction and CAL gain were reported by the investigators. The results of the test that was used to assess heterogeneity revealed that there was substantial heterogeneity across the studies in reporting the outcomes of PPD reduction (p<0.001) and moderate heterogeneity in reporting the outcome of CAL gain (p=0.085). Pooled estimates showed that regenerative material used in combination with papilla preservation flaps had 0.83mm (95 percent confidence interval [CI], 0.31 to 1.36) more PPD reduction than the use of papilla preservation flap alone, there was a high statistical difference between the two treatment groups (p=0.002) (Figure 2A). For CAL gain, 0.84mm (95 percent CI, 0.46 to 1.23) more was attained than that of papilla preservation flap alone and there was a high statistical difference between the two treatment groups (p < .001) (Figure 2B).

Subgroup analysis. In the 6M group, there were three RCTs [32],[33],[35] with parallel design and three RCTs [23],[29],[31] with split-mouth design. A subgroup analysis was performed to investigate the effect of the study design on clinical outcomes.

Pooled estimates of studies that used the split-mouth design revealed significantly more CAL gain with the use of papilla preservation flaps combined with regenerative biomaterial than with papilla preservation alone (p<0.001) and the results were robust, with no evidence of heterogeneity across the trials (p=0.37) (Table 2). Pooled estimates of studies using the parallel design did not reveal a significant difference concerning CAL gain between groups (p=0.18).

Pooled estimates of studies that used the split-mouth design revealed significantly more PPD reduction with the use of papilla preservation flaps combined with regenerative biomaterial than with papilla preservation alone (p<0.001) and the results were robust, with no evidence of heterogeneity across the trials (p=0.58) (Table 2). Pooled estimates of studies using the parallel design did not reveal a significant difference concerning PPD reduction between the two treatment groups (p=0.36).

Surgical Procedure: In the 6M group, there were three RCTs [32],[33],[35] whose investigators used the minimally invasive surgical technique and two RCTs [23],[31] whose investigators used the simplified papilla preservation flap technique (microsurgical access) to treat periodontal intrabony defects. Based on this situation, we performed a subgroup analysis to explore whether different methods of papilla preservation flaps procedures performed were clinically crucial to the outcomes. Using a fixed-effects model, pooled estimates of studies that used simplified papilla preservation flap (microsurgical access) revealed significantly more PPD reduction and CAL gain with regenerative biomaterials than with papilla preservation alone (p<0.001) with no evidence of heterogeneity across the trials (Table 2). Pooled estimates of studies that used the minimally invasive surgical technique did not reveal a significant difference concerning PPD reduction and CAL gain between groups.

12M group: Data for the 12M group meta-analysis was available from 13 trials. Out of 1004 defects, 519 defects were treated randomly by papilla preservation flap with the regenerative biomaterial and 485 defects were treated using papilla preservation flap alone. Pooled estimates in a random-effect model showed that papilla preservation flap with regenerative biomaterial had 1.19mm (95 percent CI, 0.81 to 1.57) more PPD reduction than papilla preservation flap alone (Fig.3A). There was a high statistical difference between the two treatment groups (p<0.001). Pooled estimates in a random-effect model showed that the papilla preservation flap with regenerative biomaterial had 1.4mm (95 percent CI: 1.01 and 1.83) more CAL gain than papilla preservation flap alone (Fig.3B), there was a high statistical difference between the two treatment groups (p<0.001) and the results revealed a significant heterogeneity across the trials (p<0.001).

Subgroup analysis: In the 12M group, there were nine RCTs with parallel design and four RCTs with split-mouth design. Pooled estimates regarding PPD reduction and CAL gain of studies with different designs were consistent with the combined analysis, indicating that different study designs did not affect the clinical outcomes in the long-term followup (Table 2).

There were four RCTs with papilla preservation that used GTR biomaterial and six RCTs with papilla preservation that used EMD. Pooled estimates regarding PPD reduction and CAL gain of studies with GTR and EMD were consistent with the combined analysis, indicating that different regenerative biomaterials did not affect the clinical outcomes (Table 2).

IV. Discussion

Delay in wound healing and subsequent exposure of the regenerating area have been commonly reported and associated with limited clinical outcomes[37-39]. This ill-favored occurrence is more frequent when biomaterials like barrier membranes and bone substitutes are used[13],[23],[33],[41-43]. To reduce the

delay in wound healing, various advanced flap designs have been introduced, such as papilla preservation flaps [1],[2],[45] and minimally invasive surgical approaches without papilla elevation[6],[7] or with papilla elevation [5]. All these approaches are designed to provide protection of the regenerating area and to facilitate the stabilization of blood clots.

Basic and clinical research has shown that the absolute requirements for successful regeneration of periodontal tissue include the presence of space for the blood clot formation at the interface between the flap and the root surface [44],[46-51], the blood clot stabilization to maintain stability with the root surface avoiding formation of a long junctional epithelium,[47],[52-54] and the soft-tissue protection of the treated area to prevent bacterial contamination [38],[41-43],[55-57]. The enhancement of periodontal-regenerative medicine in the past has followed two distinguishing, yet completely interlinked paths. The interest of investigators has so far concentrated on regenerative materials or products on one hand and novel surgical techniques on the other.

The evidence of clinical efficacy of regenerative biomaterials in intraosseous defects has been synopsized, over the years, in meta-analyses only for enamel matrix derivative [16],[58-60],[73],[74].

Space and stabilization of blood clot are self-provided in the so-called 'containing defects,' the narrow three-wall defects in particular [28],[61-65]. The 'non-containing defects' – the large one- or two-wall defects need an intervention to supplement the anatomic defects [20],[22],[24], [66-68]. The further use of regenerative biomaterials has to be implemented in the correction of anatomic defects [75],[76]. The equivalent goal may also be attained by implementing particular surgical approaches in which tissues are minimally elevated to enhance their stability (the minimally invasive surgical technique (MIST) and the modified minimally invasive surgical techniques (M-MIST). The protection of the regenerating site should be provided through the application of specially designed surgical strategies. The various surgical approaches developed over time involve alterations in terms of flap design and suturing technique[13]. Briefly, the traditional papilla preservation flaps did not include the mechanical properties to improve wound stability and the capacity to provide space for regeneration. In contrast, the minimally invasive surgical technique[5],[40] was designed to limit flap extension and mobility as much as possible and to enhance the ability for primary wound closure and blood clot stability. This potential was partly focused on studies that demonstrated a limited impact of the number of residual bony walls and the defect width on the outcomes obtained with regenerative biomaterials under a minimally invasive surgical technique[69-72]. It was recently confirmed in a comparative study indicating similar outcomes between the minimally invasive surgical technique alone and the minimally invasive surgical technique combined with the regenerative biomaterial [33].

Surgical access to the intrabony defects were selected from three different surgical approaches: the simplified papilla preservation flap, the modified papilla preservation technique and the crestal incision. The simplified papilla preservation flap is chosen whenever the width of the interdental space greater than 2mm, as measured at the level of the supracrestal portion of the papilla. The modified papilla preservation technique is used at sites with an interdental width of less than 2 mm and the crestal incision is applied next to an edentulous area. Whenever a defect includes one or two sides of a root and is cleansable from a minimal buccal window, the modified minimally invasive surgical technique is used. In some circumstances the modified minimally invasive surgical technique can be employed to both the interdental spaces neighboring the defect-associated tooth, permitting for instrumentation of a defect involving upto three sides of root. If the defect is not cleansable from the buccal window, the papilla is elevated, applying a minimally invasive surgical technique [2],[45].

The findings from the present meta-analysis have demonstrated significantly better CAL gain and PD reduction in the defects treated with papilla preservation flaps combined with regenerative biomaterial when compared with the papilla preservation flap alone. The results of the present meta-analysis must be interpreted with caution. In this meta-analysis, the outcomes of regenerative surgery performed in defects with different types of morphology (i.e., one-, two- and three-walled and combinations thereof), using different types of regenerative biomaterial have been combined.

Recent studies suggested that flap design may have an impact on treatment outcomes in periodontal regeneration [77],[78]. Table 1 has provided information about flap design in each treatment arms of included studies. In this meta-analysis, two separate analyses were conducted according to the length of the follow-up, as well as subgroup analysis regarding the study design, the surgical procedure and the type of biomaterial used.

In the 6M group, substantial heterogeneity was detected in the analysis of PPD reduction and moderate heterogeneity in the analysis of CAL gain. This heterogeneity may be due to the use of different study designs and surgical trials. In the 6M group, three trials used split-mouth and three trials used parallel design. Subgroup analysis results suggested that pooled estimates of studies with split-mouth design regarding CAL gain and PPD reduction were consistent with the combined analyses, showed a statistical difference between the groups. Pooled estimates with parallel design regarding CAL gain and PPD reduction did not show a statistical difference between the groups.

In the 6M group, two trials used simplified papilla preservation flap (microsurgical access) and three trials used the MIST. The pooled estimates of studies that used simplified papilla preservation flap

(microsurgical access) revealed significant PPD reduction and CAL gain in between treatment groups. The combined estimates of the studies that used MIST with and without regenerative material showed no significant difference between the treatment groups. This subgroup analysis may lead to the conclusion that different surgical techniques performed before regenerative materials were used may have an effect on the heterogeneity across the trials in this group.

In the 12 M group, in the subgroup analysis, pooled estimates regarding PPD reduction and CAL gain of studies with different study designs and regenerative materials, were consistent with combined analyses, indicating that they did not affect clinical outcomes.

The study design was considered in the subgroup analysis because it has been speculated that protection from bias could be more likely in split-mouth studies[14]. For instance, selection bias might be a minor risk as the patient provides both experimental groups. Likewise, split-mouth studies might help in upholding the masking of the patient, clinician, and examiner[14]. On the contrary, the cross-over effect is not insignificant in split-mouth studies and this effect could lessen the difference in results between interventions and shift the outcome towards null[79]. An explanation for the heterogeneity in PPD and CAL measurements might be inconstant between studies in prognostic factors that have been proved to affect the outcome of periodontal regenerative surgery. These factors include, but are not restricted to, patient-associated factors, such as smoking, compliance with oral hygiene instructions, residual inflammation after cause-related therapy, the incidence of systemic diseases and comorbidities, plaque levels, defect severity and surgical dexterity and practice of the operator[80]. Some studies present full-mouth plaque scores, other investigations present plaque scores at specific sites and some other studies show no plaque data. Therefore, the degree to which one can effectively address the heterogeneity issue might be limited. Smoking has well-documented harmful effects on the periodontal status and regenerative treatments[80-83], but most of the studies included herein did not report adequate data regarding the patient smoking status.

The analysis has some limitations as well. More long-term analysis is required to evaluate whether teeth with regenerative periodontal treatments provide better function and quality of life. The second was that the sample size and type of regenerative material were different across the included studies. Another limitation was that the reviews on novel methods of papilla preservation flap techniques like Entire papilla preservation technique and Non-incised papilla preservation surgical approach were not included due to lack of randomized control studies. Finally, due to the lack of proper studies, the funnel plot was not done to assess publication bias.

V. Conclusion

High heterogeneity among the studies restrained drawing definite conclusions. Within the limitations, results of the meta-analysis of RCTs revealed that during a short-term (6M) follow-up, the use of combination therapies had better clinical outcomes regarding PPD reduction and CAL gain compared with papilla preservation flap alone. In a long-term follow-up (12M) additional pocket reduction and clinical attachment gain were detected. The 6M group sub-analysis concerning surgical technique revealed no significant difference between the minimally invasive surgical approach with and without regenerative biomaterial, indicating the importance of cost-benefit analysis when deciding about a therapeutic approach. For obtaining favorable outcomes, a further study on the intrinsic tissue healing of minimally invasive surgical procedures without biomaterials is mandatory.

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Table 1: Characteristics of the included studies.

AUTHOR, YEAR	STUDY DESI GN	TYPE OF INTRABONY DEFECTS	TREATMENT GROUPS	AGE, YEARS (SD)	TOTAL DEFECTS, NO.	FEMALE, %	DURATION, MONTHS
Cortellini, Tonetti et al., [20]2001	Parallel	1-,2-or 3 wall	SPPF/MPPT+ GTR SPPF/MPPT	46(9.9) 46.6(11.7)	55 54	63.9	12
Zucchelli et al., [21] 2002	Parallel	1-,2-or 3 wall	SPPF/MPPT+ GTR SPPF/MPPT	48.2(7.4)	30 30	54.4	12
Tonetti et al., [22] 2002	Parallel	1-,2-or 3 wall or combination	SPPF/MPPT+EMD SPPF/MPPT	48(9) 48(9)	83 83	57.2	12
Wachtel et al., [23] 2003	Split mouth	1-,2-or 3 wall or combination	SPPF/MPPT+EMD SPPF/MPPT (microsurgical access)	28-65	26 26	72	6 & 12
Tonetti et al., [24] 2004	Parallel	2-or 3 wall or combination	SPPF/MPPT+ GTR SPPF/MPPT	49.5(11) 51(10.5)	61 59	61.5	12
Francetti et al., [25] 2004	Parallel	1-,2-or 3 wall or combination	SPPF/MPPT+EMD SPPF/MPPT	-	12 12	-	12 & 24
Francetti et al., [26] 2005	Parallel	1-,2-or 3 wall or combination	SPPF/MPPT+EMD SPPF/MPPT	43.8(8.3) 44.6(8.1)	82 55	56.7	12 & 24
Aimetti et al., [27] 2005	Split mouth	Predominantly one wall defect	SPPF/MPPT+ GTR SPPF/MPPT	48.28(8.5)	18 18	44	12
Linares et al., [28] 2006	Parallel	-	SPPF/MPPT+ GTR/DBBM SPPF/MPPT	49.5(11.3) 51(10.5)	57 53	63.7	12
Heinz et al., [29] 2009	Split mouth	2 wall defects	SPPF/MPPT+ GTR/DBBM SPPF/MPPT	38-40	14 14	57.14	6
Stein et al., [30] 2009	Parallel	1-,2-or 3 wall	SPPF/MPPT+ BIOMATERIAL BONE GRAFT SPPF/MPPT	46.3(7.1) 45(10.5)	15 15	68.9	12
Fickl et al., [31] 2009	Split mouth	1-,2-or 3 wall	SPPF/MPPT+EMD SPPF/MPPT (microsurgical access)	46.1	35 35	68.4	6 & 12
Trombelli et al.,[32]2010	Parallel	1-,2-or 3 wall	SFA+GTR SFA (MIST)	45.6(8.5) 56.3(5)	12 12	29	6
Ribero et al., [33] 2011	Parallel	-	SPPF/MPPT+EMD SPPF/MPPT(MIST)	47.1(6.9)	14 15	66	6
Cortellini et al.,[34]2011	Parallel	1-,2-or 3 wall or combination	SPPF/MPPT+EMD SPPF/MPPT (MIST)	48.9(7.9) 47.2(8.5)	15 15	47	12
Mishra et al., [35] 2013	Parallel	2- or 3- wall or combination	SPPF/MPPT+rhPDGF SPPF/MPPT (MIST)	25-50	11 11	50	6
Santana et al., [36] 2015	Splitmouth	1-,2-or 3 wall or combination	SPPF/MPPT+rhFGF-2/HA SPPF/MPPT	39-66	30 30	-	12

SPPF: SIMPLIFIED PAPILLAPRESERVATIONTECHNIQUE
MPPT: MODIFIED PAPILLAPRESERVATION TECHNIQUE
EMD: ENAMEL MATRIXDERIVATIVE
MIST: MINIMALLY INVASIVE SURGICAL TECHNIQUE
SFA: SINGLE FLAP APPROACH
GTR: GUIDED TISSUE REGENERATION
DBBM:DEPROTEINIZED BOVINE BONE
rhFGF-2: RECOMBINANT HUMAN FIBROBLAST GROWTH FACTOR-2
HA: HYDROXYAPATITE

Table 2: Subgroup analysis regarding the study design, surgical procedure and regenerative material.

SUBGROUP	SUBGROUP (NO. OF PARTICIPANTS)	MEAN DIFFERENCE, 95% CONFIDENCE INTERVAL	Z SCORE	P VALUE	HETEROGENEITY		
					Chi-square	*P* Value	I^2, %
Analysis in the 6M Group **Study Design**							
Split-mouth design	3 trials (150)						
PPD* reduction		1.33 (1.30 to 1.48)	29.64	<.001	2	.58	0
CAL† gain		1.1 (0.96to 1.24)	15.77	<.001	2	.37	0
Parallel design	3 trials (74)						
PPD reduction		0.23 (-0.27 to 0.73)	0.91	.36	2	.80	0
CAL gain		0.84 (0.46 to 1.22)	1.34	.18	2	.99	0
Surgical Procedure Simplified Papilla Preservation (microsurgical access)	2 trials (122)						
PPD reduction		1.39(1.3 to 1.5)	29.52	<.001	1	.3	0
CAL gain		1.08(0.95 to 1.23)	15.48	<.001	1	.41	0
Minimally Invasive surgical technique	3 trials (75)						
PPD reduction		0.23(-0.3 to 0.73)	0.91	.36	2	.80	0
CAL gain		0.35(-0.16,0.86)	1.34	.18	2	.99	0
Analysis in the 12M Group **Study Design**							
Split mouth design	4 trials (218)						
PPD reduction		1.80(1.30 to 2.3)	7.10	<.001	13.89	<.003	78
CAL gain		1.42 (1.01,1.83)	8.33	<.001	29.13	<.001	90
Parallel Design	9 trials (766)						
PPD reduction		0.9(0.54 to 1.26)	4.9	<.001	62.88	<.001	87
CAL gain		1.17(0.83 to 1.51)	6.77	<.001	46.8	<.001	82
BIOMATERIAL	4 trials (164)						
GTR							
PPD reduction		1.12(0.37 to 1.87)	2.91	.004	21.03	<.001	86
CAL gain		1.35 (0.81 to 2.06)	3.72	<.001	17.76	<.001	83
EMD	6 trials (253)						
PPD reduction		1.21(0.68 to 1.73)	4.5	<.001	82.5	<.001	91
CAL gain		1.34(0.81 to 1.87)	4.9	<.001	52.5	<.001	94

PPD- POCKET PROBING DEPTH
CAL- CLINICAL ATTACHMENT LEVEL
GTR- GUIDED TISSUE REGENERATION EMD- ENAMEL MATRIX DERIVATIVE

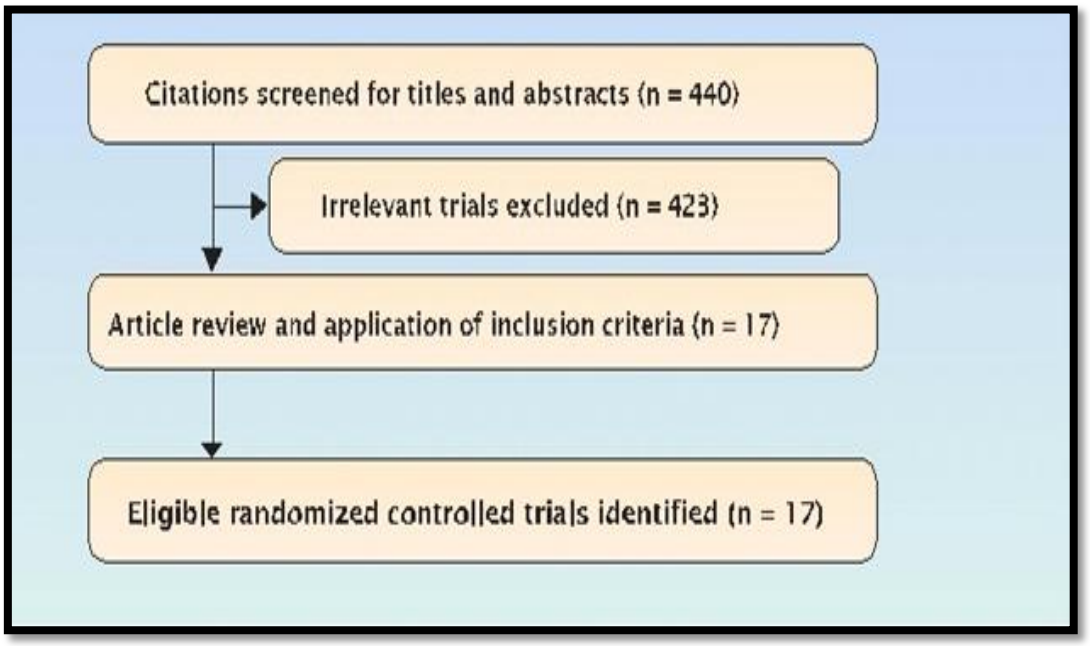

Figure 1: Study flow of the meta-analysis.

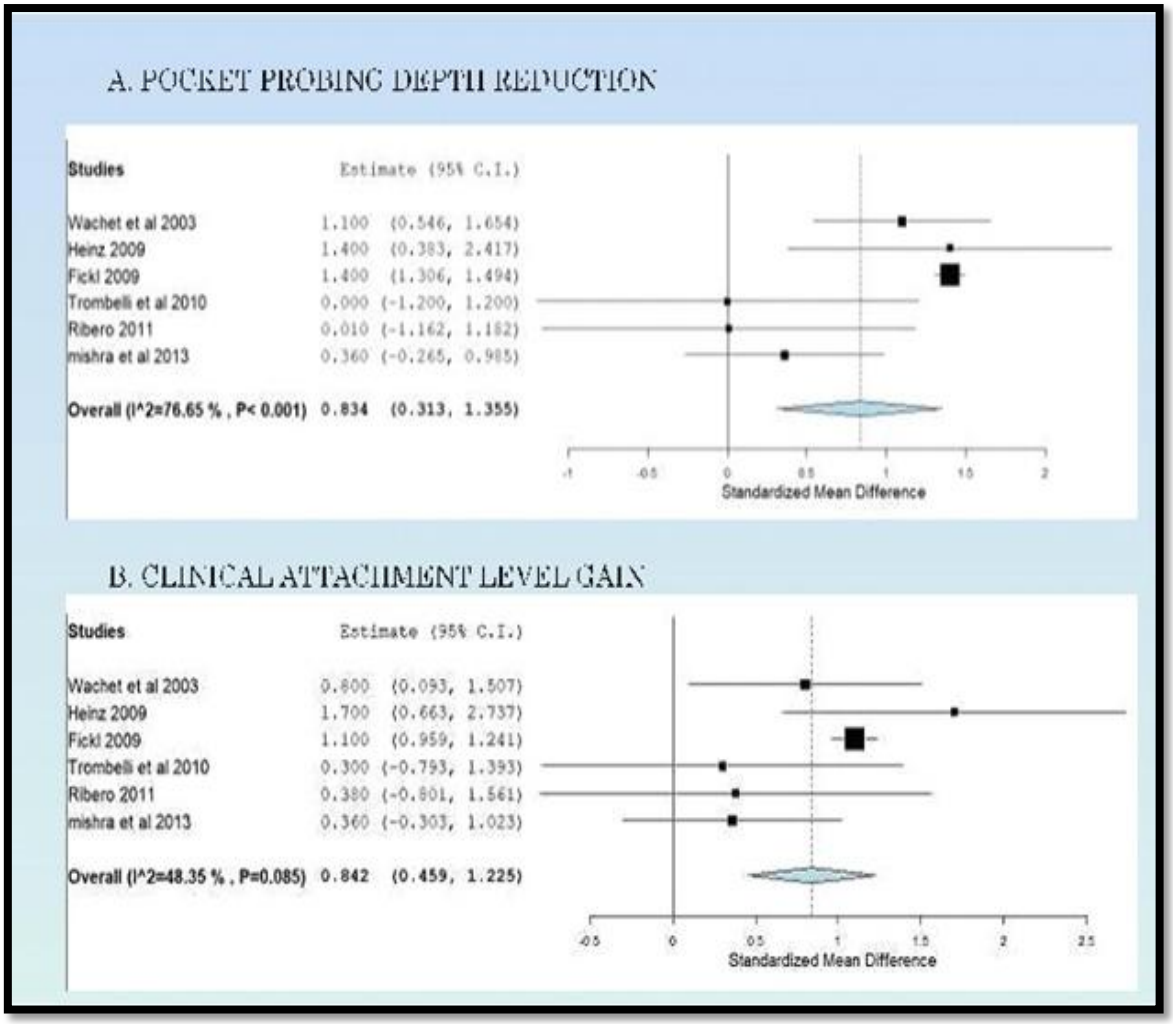

Figure 2: Forest plot of the meta-analysis for 6M group for parameters pocket probing depth reduction *(above)* and clinical attachment level gain *(below).*

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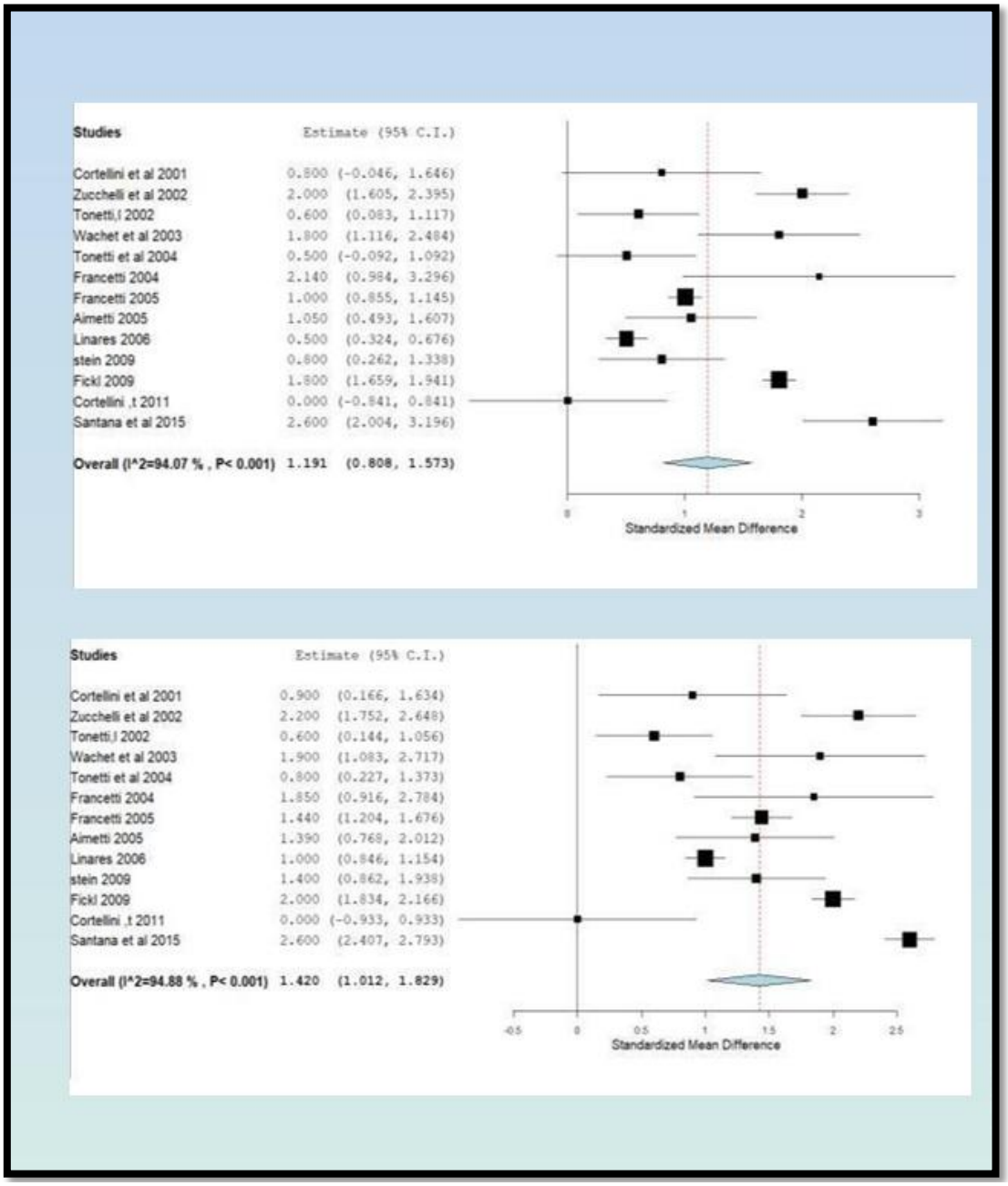

Figure 3: Forest Plot of the meta-analysis in12M group for parameters pocket probing depth reduction *(above)* and clinical attachment level gain *(below)*.

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