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Systematic Review

Predictability and Clinical Stability of Barrier Membranes in Treatment of Periodontal Intrabony Defects: A Systematic Review and Meta-Analysis

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Abstract: The adjunctive use of GTR membranes helps us to achieve predictable periodontal regeneration. The aim of this systematic review was to evaluate and compare the treatment efficacy of resorbable versus non-resorbable barrier membranes used in guided tissue regeneration in the treatment of intrabony defects in chronic periodontitis patients. The following databases were searched: Medline, the Cochrane Central Register of Controlled Trails (CENTRAL), SCOPUS, EMBASE. Randomized clinical trials (RCTs) published in English languages over the past 25 years were included. The primary outcomes assessed were: change of probing pocket depth (PD), change in clinical attachment level (CAL) and gingival recession coverage (GRC), and intrabony defect fill (IBDF). A total of eight RCTs were included for systematic review. The outcome of GR at a six-month interval revealed a significant difference in treatment effect with a mean difference of 0.42, 95% CI [0.02, 0.81]; Z = 2.09, (p = 0.04) favouring the resorbable membrane group. The intrabony defect depth fill at a 12-month interval revealed a significant difference in treatment effect with MD of 0.79, p = 0.00001; favoring the resorbable membrane group. The resorbable membrane showed a significant improvement in gingival recession coverage and intrabony defect fill, owing to its advantage of avoiding the second surgical intervention.

Keywords: guided tissue regeneration; barrier membrane; bony defects; periodontal regeneration; systematic review; meta-analysis

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1. Introduction

Periodontitis is a condition which leads to the inflammation and loss of periodontal tissue (alveolar bone, periodontal ligament, and cementum), which ultimately leads to tooth loss [1]. The destruction of periodontal tissue is characterized by pocket formation, attachment loss, and subsequently bone loss, leading to teeth mobility [2]. Periodontal regeneration is defined as "the reproduction or reconstruction of lost or injured tissue so that the form and function of the lost structures are restored" [3].

Clinicians currently prefer the use of a variety of biomaterials for achieving periodontal regeneration, namely autogenous bone grafts [4], calcium sulphate [5], chitosan [6], demineralized freeze-dried bone graft [7], xenografts [8], barrier membranes of different types with combination of bone grafts [9], enamel matrix derivatives [10], and platelet rich fibrins [11]. Recent advances in biomaterials and regenerative dentistry have led to the use of three-dimensional hydrogels (collagen, chitosan, hyaluronic acid-based) for periodontal regeneration [12]. Moreover, systematic reviews have suggested that autologous

platelet concentrates are also used, along with other regenerative materials, or alone in the treatment of intra-bony defects [13], furcation defects [14], and alveolar sockets [13].

However, a particular concern for many patients is that conventional regenerative surgery tends to increase gingival recession, further leading to cosmetic problems. In an attempt to overcome some limitations of the conventional procedures, Melcher, in 1976, proposed that periodontal ligament cells are regarded as one of the most regenerative cells, which when allowed to proliferate, would aid in both cementogenesis, collagen synthesis, and osteogenesis, which further aids in the attachment of newly formed collagen fibers of periodontal ligament or lamina propria to teeth in normal conditions [15]. Thus, placing a non-resorbable or bio-degradable barrier membrane could exclude certain cell types such as rapidly proliferating epithelium and connective tissues, thus promoting the slower growing cells which are responsible for the regeneration of bone [16]. Most GTR cases have shown healing with the formation of new attachments [17]. In this procedure, a biocompatible barrier membrane (either resorbable or non-resorbable) is surgically implanted to cover and protect the bone defect. If non-resorbable, the barrier is surgically removed 4 to 6 weeks after implantation. Connective tissue and bone regeneration may then occur within the bone defect protected by the barrier.

Current treatment modalities for treating advanced periodontal defects are not able to completely restore the soft and hard tissues surrounding the tooth. The guided tissue regeneration technique may be able to achieve regeneration, and henceforth allows the clinician to achieve regeneration and improve conventional surgical procedures. It was seen in a multicenter randomized controlled trial that the use of regenerative periodontal surgery with a GTR offers an additional benefit in terms of CAL gains, PPD reductions, and the predictability of outcomes with respect to papilla preservation flaps alone [18]. It was also suggested that these regenerative barriers along with bone grafts also result in more clinical benefits than OFD alone [19].

Previous systematic reviews conducted on the GTR membrane showed that, irrespective of the type of membrane used, regenerative therapy using a barrier membrane always produces better results in terms of improving clinical parameters when compared to OFD [20]. The advantages of using GTR membranes are that resorbable membranes do not require a second surgical site and reduce patient morbidity, help in soft tissue healing [21], show tissue friendly reactions to membrane exposure, and are cost-effective. However, the uncertain resorption time of these membranes [22], the inflammatory response from tissues [23,24], and technique sensitivity can be considered disadvantages of the resorbable membrane. To the best of our knowledge, there is an inadequacy in studies that compared and systematically evaluated the efficacy of resorbable and non-resorbable membranes in periodontal intra-bony defects for guided tissue regeneration. This is a first-of-its-kind systematic review evaluating and comparing the clinical and radiological parameters in periodontal defects treated with the resorbable and non-resorbable barrier membranes alone, and with a combination of bone grafts.

The aim of the current systematic review is to evaluate and compare the clinical outcomes of different varieties of resorbable and non-resorbable GTR membranes in periodontal intra-bony defects, which might have some guiding role in the clinical management strategy.

2. Materials and Methods

This systematic review was structured and conducted according to the Preferred Reporting of Systematic Reviews and Meta-analyses (PRISMA) statement. The protocol of this systematic review was registered under Prospero registration no. CRD42020196628.

2.1. Eligibility Criteria

This review only considered randomized controlled clinical trials with a minimum 6-month follow-up period. The research question was formulated by using the PICO format (P—patient or population, I—intervention, C—comparison, O—outcome). The

PICO question was: "What is the difference in treatment effect of resorbable versus non resorbable barrier membrane in surgical management of periodontal intra-bony defects?"

The participants who were included in the studies had received clinical diagnoses of chronic periodontitis, based on the international classification of periodontal diseases. Another important criterion was that those patients should have intra-bony defects in either the maxilla or mandible. The studies, which included patients having aggressive periodontitis, were eliminated from this systematic review.

Randomized controlled clinical trials with minimum 6-month follow-up periods, with patients who had undergone the open flap debridement of intra-bony defects in either the maxilla or mandible, with the placement of resorbable or non-resorbable membranes as a regenerative treatment strategy for the management of intra-bony defects, were included.

There was the presence of an appropriate control group, in which the same therapeutic procedures as those employed in at least one experimental group were clinically applied for the treatment of intra-bony defects, without the adjunctive effect of the GTR membrane.

The outcome measures were as follows: baseline and post-operative defect characteristics, probing pocket depth (PPD), clinical attachment level (CAL), gingival recession coverage (GRC), and intra-bony defect depth (IBDD).

Studies done in vitro or on animals were excluded from the study, as well as studies reporting case series, case reports, aggressive periodontitis cases, and patients with systemic diseases.

2.2. Search for Identification of Studies

We searched the Medline, the Cochrane Central Register of Controlled Trails (CENTRAL), Scopus, EMBASE till January 2022 using the search keywords "guided tissue regeneration" [All Fields] OR "gtr" [All Fields]) OR "bioresorbable membrane" [All Fields]) OR "non-resorbable membranes" [All Fields]) OR "barrier membranes" [All Fields]) OR "collagen membranes" [All Fields]) OR "periodontal regeneration" [All Fields]) OR "regenerative therapy" [All Fields]) AND "infrabony defects" [All Fields] OR "intrabony defects" [All Fields]) OR "intraosseous defects" [All Fields]) OR "bony defects" [All Fields]) OR "two walled defects" [All Fields]) OR "three walled defects" [All Fields])) AND "chronic periodontitis" [All Fields] OR "periodontitis" [All Fields]) OR "periodontal infection" [All Fields]) OR "periodontal inflammation" [All Fields]) OR "periodontal disease" [All Fields]) OR "parodontitis" [All Fields]). In addition, a hand search was performed in the following dental journals: *British Dental Journal*, *International Journal of Periodontics and Restorative Dentistry*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Dentistry*, *Journal of Periodontal Research*, *Indian Journal of Periodontology*. The MEDLINE search was adapted for use in searching the other databases.

2.3. Screening and Selection of Studies

Two independent reviewers (S.D. and R.N.) screened the titles and abstracts in accordance with the inclusion criteria mentioned earlier. Upon independent screening, full-text versions of all eligible articles for this systematic review were downloaded and scrutinized by both reviewers for final selection. Any disagreements between the reviewers were resolved by open discussion while including the articles. In the case of an unresolved disagreement, an expert arbiter (S.P.) was further consulted. After the final selection, the included studies were subjected to data extraction.

2.4. Data Extraction and Analysis

Data extraction was performed independently by two reviewers (S.D. and R.N.) using the selected articles. The relevant data of the included studies were extracted in detail, using an Excel spreadsheet (Microsoft, Redmond, WA, USA, Version 2007). The extracted data included: year of publication, type of study, author, country, age group, defect characteristics, no. of patients included, no. of sites included, surgical procedure used in both test and control group, biomaterials used in both test and control groups,

trade name of the biomaterials, parameters or outcomes which were assessed after the surgical procedure. The random effects models were applied during meta-analysis to account for methodological differences among studies. Forest plots were produced to graphically represent the confidence interval (CI) for the primary outcomes. Heterogeneity was assessed by using the Tau^2 test, Chi-square test and I^2 test, which ranged from 0 to 100% (lower values represent less heterogeneity). The reporting of these meta-analyses adhered to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) statement.

2.5. Risk of Bias Assessment

The RevMan risk of bias tool was used to evaluate the quality assessment of the studies included. The criteria, which were used to estimate the quality of selected randomized controlled trials (RCTs), were: formation of randomization sequence, allocation concealment, blinding of the operators and examiner, addressing insufficient outcome data, loss of follow-up (attrition bias), and free of selective outcome reporting. For every domain, risk was classified as low, unclear, or high. The level of bias was classified as: low risk when all the requirements were met, unclear risk when one criterion was missing, and high risk if two or more criteria were missing. Finally, all the included studies were evaluated by two independent reviewers (S.D. and R.N.).

3. Results

3.1. Selection of Studies

A total of 4063 reports were identified through the electronic and manual search for screening after discarding the duplicates. The eligible reports were screened based on title/abstracts and were subjected to full-text assessments. Twenty-nine studies were excluded due to a lack of relevant information or not meeting the inclusion criteria (Table A1). The details of the study selection process are provided in Figure 1.

3.2. Characteristics of Studies

All eight studies, which were included in this systematic review, are randomized controlled trials (RCTs). Among the eight studies, 3 RCTs are split mouth, and the rest of the studies are parallel design RCTs. A total of 194 participants were included in this systematic review, and a total number of 228 defect sites were evaluated after surgical treatment. All studies mentioned the age limit of the participants (23–72 years). In addition, all eight studies reported having a follow-up period starting from 6 months till 30 ± 6 months. Two studies included other tests, such as bacterial and viral culture and interleukin level measurement. The details of the demographic and interventional criteria are given in Tables 1 and 2, respectively.

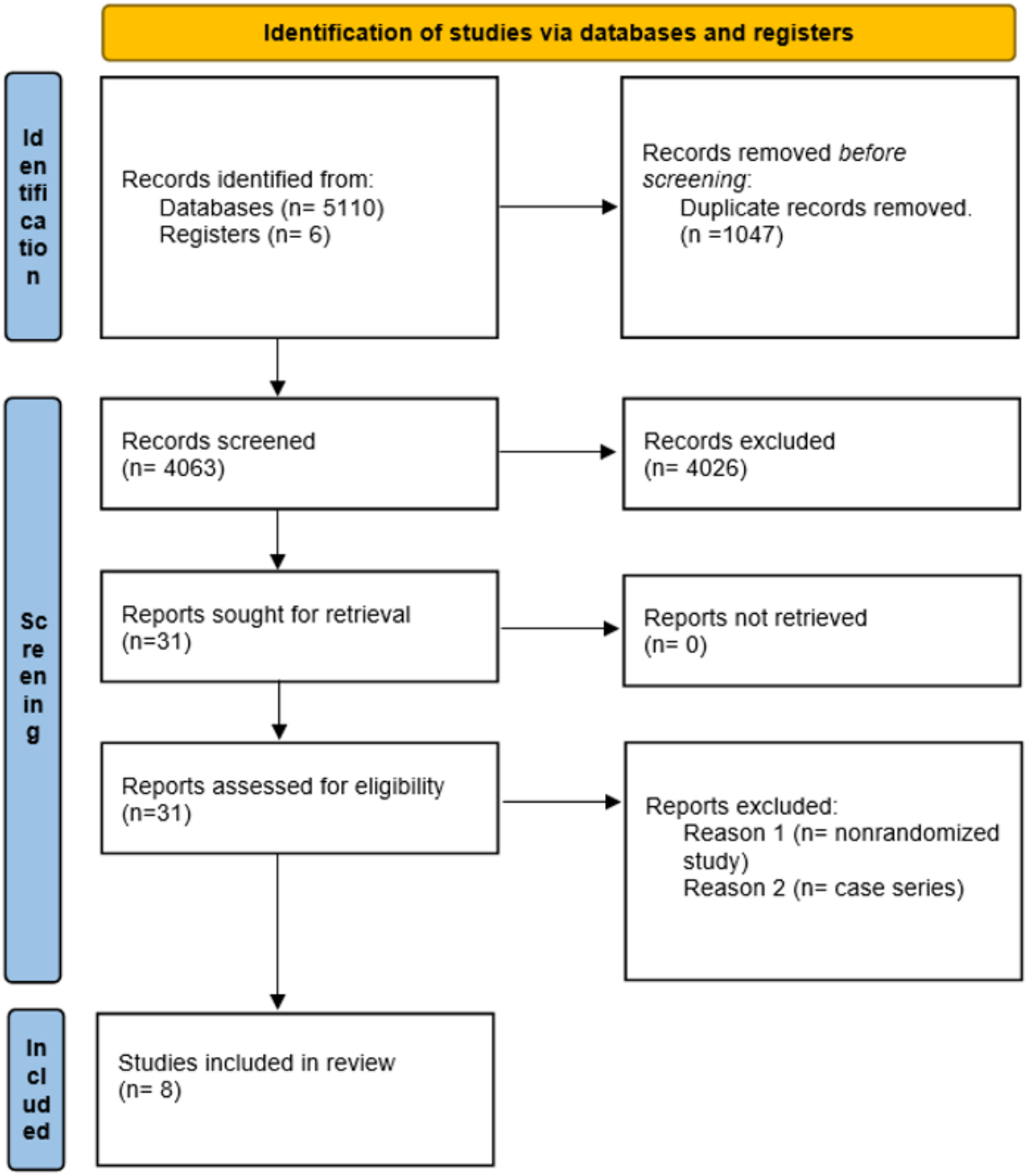

Figure 1. PRISMA 2020 flow diagram for systematic review.

Table 1. Demographic characteristics of the included studies.

Author and Year	Study Design	Age Range	Defect Characteristics	No. of Patients	No. of Sites	Test Procedure	Control Procedure	Follow-Up
Wadhaban et al., 2012 [25]	RCT split-mouth	25–55	Bilateral-matched intrabony defects with probing depth of ≥6 mm and radiographic evidence of angular bone loss	10	20	Bioresorbable membrane (Resolut Adapt®) and bioactive glass	Non-resorbable membrane (GoreTex®) and bioactive glass	3, 6, 9 months
Eickholz et al., 2007 [26]	RCT split mouth	23–64	A minimum of one defect having an infrabony component ≥ 3 mm	31	50	Polyglactin barrier, polylactide-tributylcitrate membrane, regenerative materialmembrane	Expanded polytetrafluoroethylene (ePTFE) barriers	6, 60 ± 3 months
Aichelmann-Reidy et al., 2004 [27]	RCT split mouth	>26	Two interproximal sites with probing depth ≥ 5 mm and intrabony defects ≤ 3 mm	19	38	DFDBA plus Calcium Sulfate barrier (4:1 ratio)	DFDBA plus ePTFE (Gore TEX Periodontal Membrane)	6 months
Karapataki et al., 2005 [28]	RCT parallel	43 ± 7	Intrabony defect depth = 4 mm and probing attachment level = 6 mm	19	19	Non-resorbable e-PTFE barrier (GORE-TEX Periodontal Material)	Resorbable PLA barrier (GUIDORA bioresorbable matrix barrier)	12 months
Zybutz et al., 2000 [29]	RCT parallel	48.9	Vertical intra-bony defect of at least 3 mm as assessed from standardized intra-oral radiographs	29	29	Nonresorbable membrane (ePTFE membrane)	Resorbable membrane (polylactic acid)	6, 12 months
Pontoriero et al., 1999 [30]	RCT parallel	32–61	(PPD) of >6 mm, (PAL) of >7 mm, and a depth of the intrabony component of >3 mm.	40	40	Resorbable membrane (Resolut) and Guidor membrane	Nonresorbable membrane (Gore-Tex membrane)	12 months
Smith MacDonald et al., 1998 [31]	RCT split-mouth	35–63	2 radiographically similar 2 to 3 wall interproximal intraosseous periodontal defects	10	20	Nonresorbable membrane (ePTFE membrane)	Resorbable membrane	12 months
Cortellini et al., 1996 [32]	RCT parallel	30–58	Deep intrabony defect, located in the area, was identified	36	12	Nonresorbable membrane	Resorbable membrane	12 months

Table 2. Interventional characteristics of the included studies.

Author and Year	Procedure	Test Biomaterial	Trade Name	Control Biomaterial	Trade Name	Outcomes Assessed
Wadhaban et al., 2012 [25]	OFD	RM and BG	ResolutAdapt®-W.L. Gore and Associates Inc., Flagstaff, AZ, USA	NRM and BG	Gore-Tex® membrane, W.L. Gore and Associates Inc., Flagstaff, AZ, USA	P.I, G.I., PD, CAL, GRC, IBDF
Eickholz et al., 2007 [26]	OFD	PG/PTM	Guidor matrix barrier, Resolut Ada	expanded polytetrafluoroethylene (ePTFE) barriers	Gore-Tex Periodontal Material, W. L. Gore & Associates Inc., Flagstaff, AZ	G.I, P.I, P.D, CAL
Aichelmann-Reidy et al., 2004 [27]	OFD	DFDBA + CS (4:1 ratio)	CapSet, Lifecore Biomedical, Inc., Chaska, MN.	DFDBA + ePTFE membrane	GoreTex Periodontal Membrane, W.L. Gore & Associates Inc., Flagstaff, AZ	PD, CAL, GRC, IBDD
Karapataki et al., 2000 [28]	OFD	NRM	GORE-TEX Periodontal Material	RM	GUIDORA bioresorbable matrix barrier	PD, PAL, probing bone level
Zybutz et al., 2000 [29]	OFD	NRM	Gore-Tex Periodontal Material, W. L. Gore & Associates Inc., Flagstaff, AZ	RM	Guidor Matrix Barrier, Guidor AB, Huddinge, Sweden	P.I, G.I, PPD, PAL, GR, IBD
Pontoriero et al., 1999 [30]	OFD	NRM	Gore-Tex Periodontal Material, W. L. Gore & Associates Inc., Flagstaff, AZ	RM	Guidor Matrix Barrier, Guidor AB, Huddinge, Sweden Resolut Adapt®-W.L. Gore and Associates Inc., Flagstaff, AZ, USA	PPD, PAL, GR
Smith MacDonald et al., 1998 [31]	OFD	NRM	Gore-Tex Periodontal Material, W. L. Gore & Associates Inc.Flagstaff AZ	RM	Resolut, W.L. Gore and Associates Inc.	PPD, PAL, REC, depth of osseous defects
Cortellini et al., 1996 [32]	MWF	NRM	Gore-Tex, WL. Gore and Associates Inc., Flagstaff, AZ.	RM	Flagstaff, AZ. Resolut, W.L. Gore and Associates Inc., Flagstaff, AZ.	P.I, G.I, PD, CAL, GR

3.3. Quality Analysis of the Studies

The results for the risk of bias analysis for the included studies were streamlined in Figure 2.

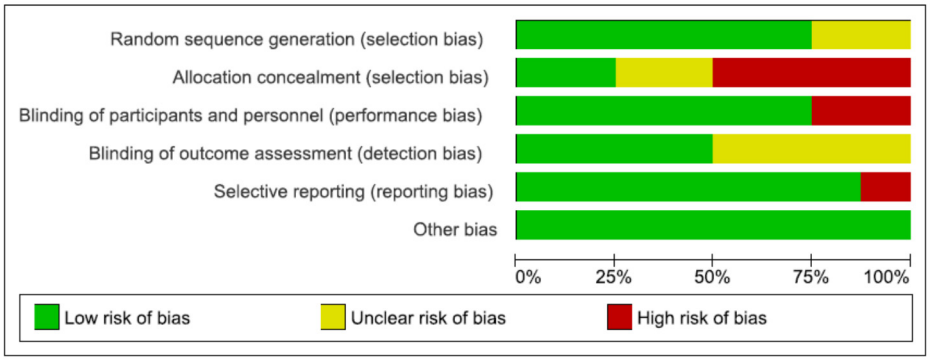

Figure 2. Risk of bias graph of the included studies.

Among the included studies, one study showed a high risk of bias [25], and one study showed a low risk of bias [27], while the rest of the studies showed a moderate risk of bias (Figure 3).

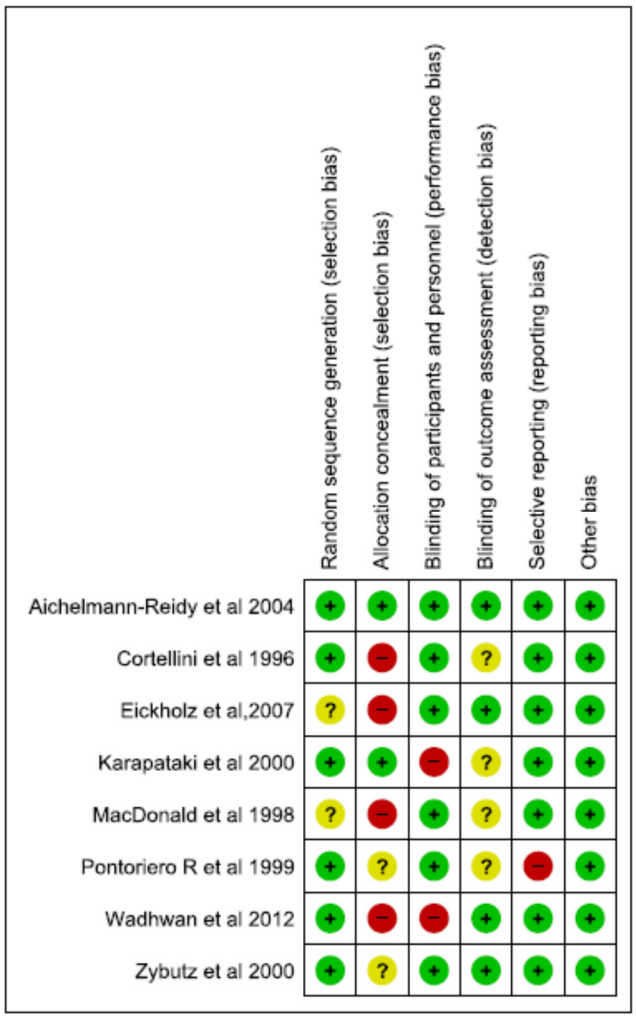

Figure 3. Risk of bias summary of all the included studies.

3.4. Meta-Analysis

The quantitative data of the included studies were subjected to a meta-analysis. A forest plot was used to pull the effect estimates of both treatment groups for similar studies with a similar outcome.

3.4.1. Meta-Analysis of Probing Pocket Depth (PPD)

A forest plot showing a comparison between resorbable and non-resorbable membrane for the assessment of the outcome of probing pocket depth at all intervals (6–12 months) reveals no significant difference in treatment effect with a mean difference of 0.69, 95% CI [−0.57, 1.95]; Z = 1.07 (p = 0.28). The heterogeneity among the studies was considerably high (Chi^2 = 191.15, I^2 = 97%) (Figure 4).

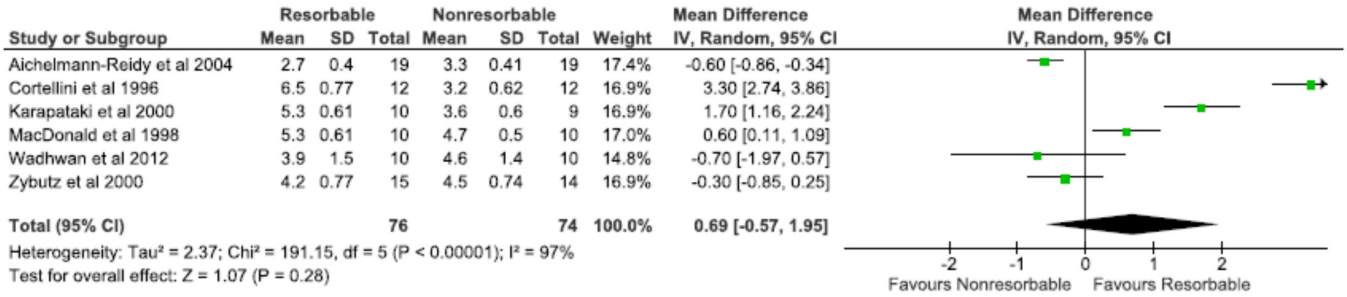

Figure 4. Meta-analysis of probing pocket depth (PPD) at all intervals (6–12 months).

3.4.2. Sub-Group Analysis for Probing Pocket Depth (PPD)

As no significant results were found while comparing the resorbable membrane group with the non-resorbable membrane group in terms of pocket probing depth, a subgroup analysis was performed based on the study design, using the included studies to evaluate any significant difference in these two groups. The subgroup analysis for probing pocket depth shows a significant difference in treatment effect in the split mouth study design group, with a mean difference of −0.60, 95% CI [−0.86, 0.35]; Z = 4.69 (p < 0.00001), when compared to parallel mouth study design group showing a non-significant difference with a mean difference of 1.32, 95% CI [−0.15, 2.80]; Z = 1.76 (p = 0.08). In the split mouth design, a significant result was seen in the non-resorbable group, whereas in the parallel mouth design, no significant result was seen. The heterogeneity is less in the studies with the split-mouth study design with Chi^2 = 0.02 and I^2 = 0% in comparison to the studies in the parallel study group with Chi^2 = 91.55 and I^2 = 97% (Figure 5).

3.4.3. Meta-Analysis for Clinical Attachment Levels (CAL)

A forest plot showing the comparison between resorbable and non-resorbable membranes for the assessment of the outcome of CAL at all intervals (6–12 months) reveals no significant difference in treatment effect, with a mean difference of −0.27, 95% CI [−1.34, 0.80]; Z = 0.50, (p = 0.62). The heterogeneity among the studies was considerably high (Chi^2 = 99.02, I^2 = 95%) (Figure 6).

3.4.4. Subgroup Analysis for Clinical Attachment Levels (CAL)

The subgroup analysis for clinical attachment level shows no significant difference in treatment effect in both the split mouth study design group with the mean difference of −0.60, 95% CI [−0.86, −0.35]; Z = 4.69, p = 0.00001, and the parallel mouth study design group showing no significant difference, with a mean difference of 1.32, 95% CI [−0.15, 2.80]; Z = 1.76 (p = 0.08) (Figure 7).

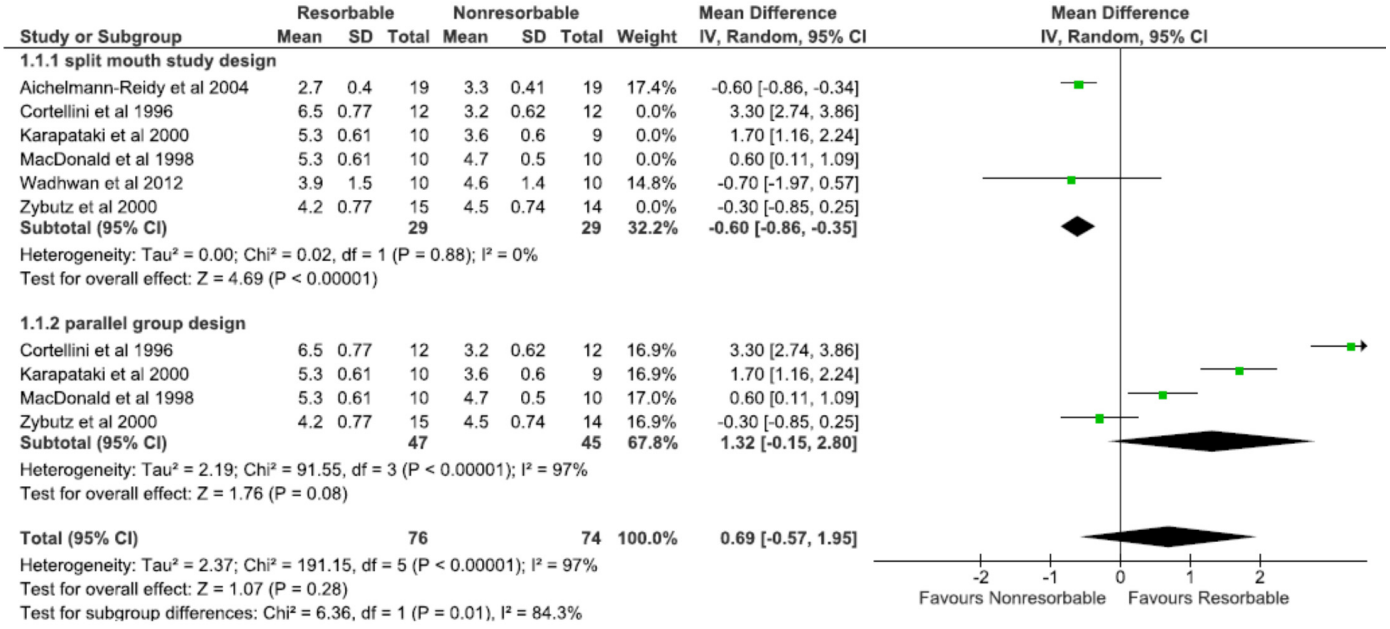

Figure 5. Subgroup analysis of probing pocket depth (PPD) at all intervals (6–12 months).

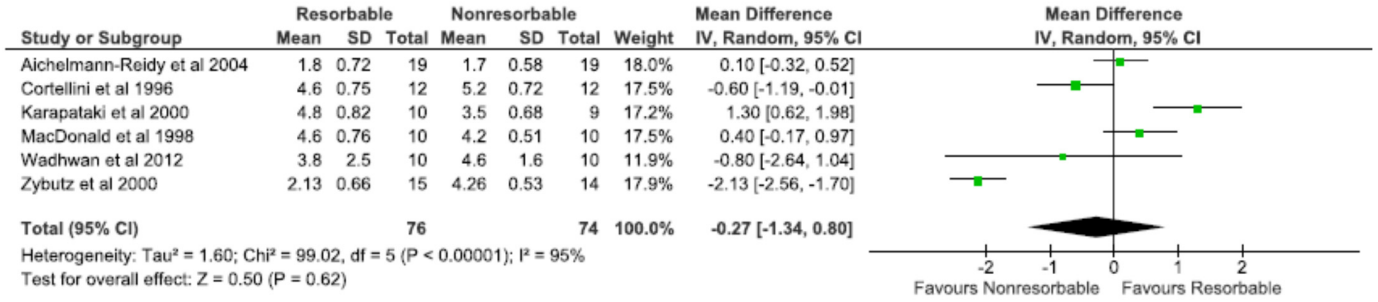

Figure 6. Meta-analysis of clinical attachment level (CAL) at all intervals (6–12 months).

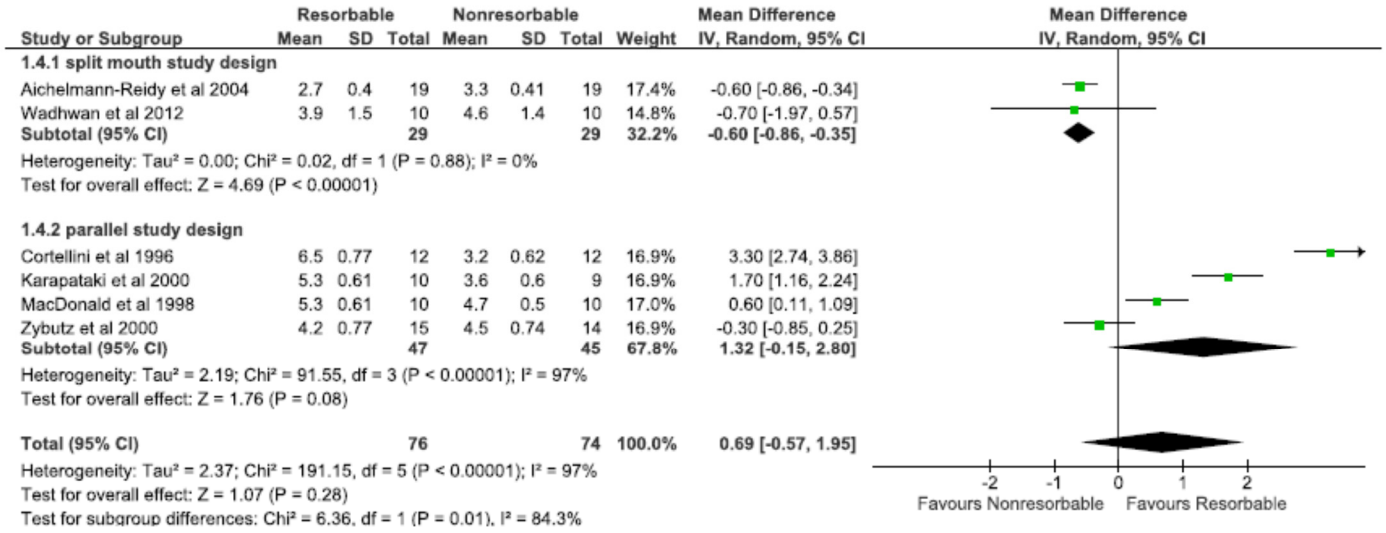

Figure 7. Subgroup analysis of clinical attachment level (CAL) at all intervals (6–12 months).

3.4.5. Meta-Analysis for Gingival Recession Coverage (GRC)

A forest plot showing a comparison between resorbable and non-resorbable membranes for the assessment of the outcome of GRC at all intervals 6–12 months reveals no significant difference in treatment effect, with a mean difference of −0.73, 95% CI [−2.09, 0.64]; Z = 1.05, (p = 0.30). The heterogeneity among the studies was considerably high (Chi^2 = 78.49, I^2 = 96%) (Figure 8).

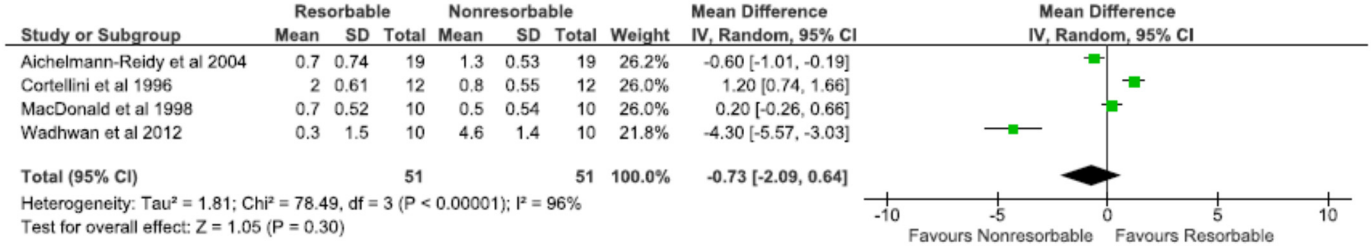

Figure 8. Meta-analysis of gingival recession (GRC) at all intervals (6–12 months).

A forest plot showing a comparison between resorbable and non-resorbable membranes for the assessment of the outcome of GR at a 6-month interval reveals a significant difference in treatment effect, with a mean difference of 0.42, 95% CI [0.02, 0.81]; Z = 2.09, (p = 0.04), favoring the resorbable membrane group. The heterogeneity among the studies was low (Chi^2 = 1.60, I^2 = 38%) (Figure 9).

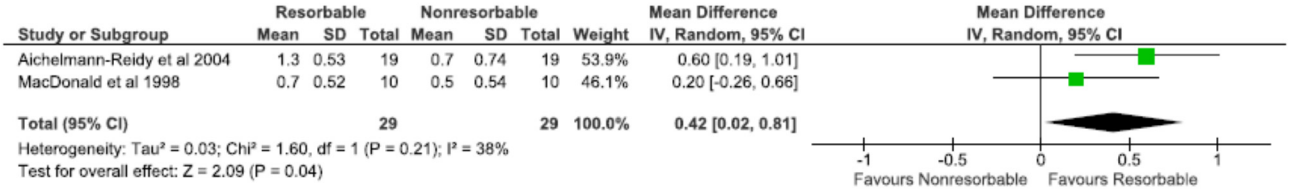

Figure 9. Meta-analysis of gingival recession (GRC) at 6 months.

3.4.6. Meta-Analysis for Intra Bony Defect Depth (IBDD)

A forest plot showing a comparison between resorbable and non-resorbable membranes for the assessment of the outcome of the IBDD at all intervals (6–12 months) reveals a significant difference in treatment effect with a mean difference of 0.65, 95% CI [0.16, 1.15]; Z = 2.61, (p = 0.009) favoring the resorbable treatment group. The heterogeneity among the studies was moderate (Chi^2 = 12.37, I^2 = 76%) (Figure 10).

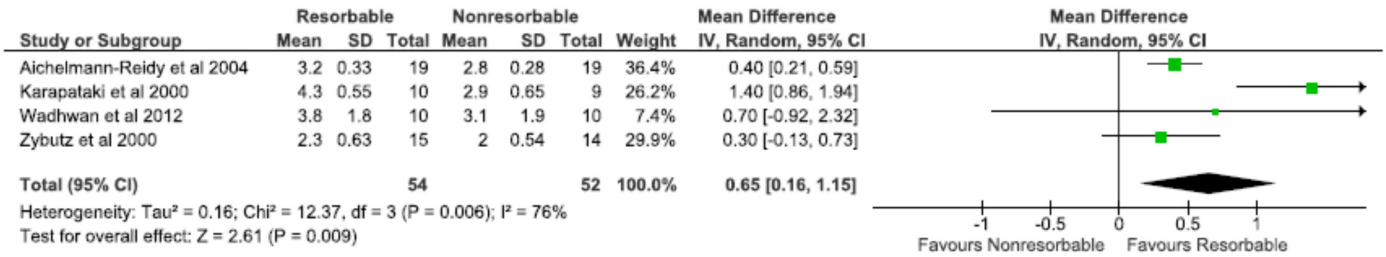

Figure 10. Meta-analysis of intra-bony defect depth (IBDD) at all intervals (6–12 months).

Two studies comparing the use of resorbable and non-resorbable membranes for regeneration of periodontal intra-bony defects were included in the meta-analysis plot to assess the treatment effect in terms of IBDD. A forest plot showing a comparison between resorbable and non-resorbable membranes for the assessment of the outcome of IBDD at a 12-month interval reveals a significant difference in treatment effect, with a mean difference

of 0.79, 95% CI [0.46, 1.13]; Z = 4.64, (p = 0.00001) favoring the resorbable membrane group. There was heterogeneity among these two studies (Chi^2 = 13.58, I^2 = 93%) (Figure 11).

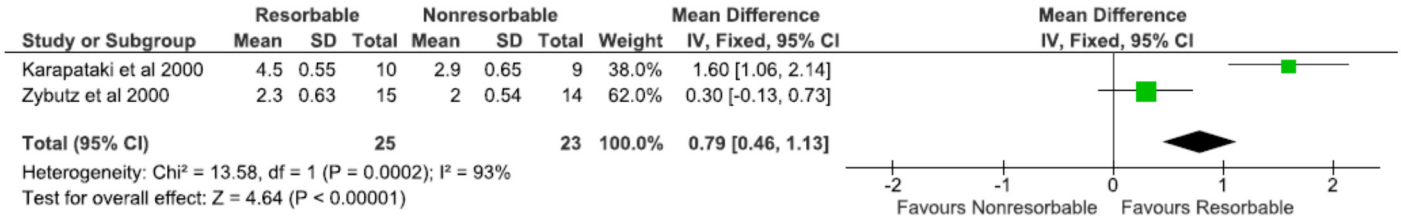

Figure 11. Meta-analysis of intra-bony defect depth (IBDD) at 12 months.

4. Discussion

This systematic review aims to assess the clinical and radiological parameter (PD reduction, CAL gain, recession coverage, bone fill), which changed from baseline after using guided tissue regenerative therapy (resorbable versus non-resorbable membranes) in the treatment of intrabony defects in chronic periodontitis patients solely relying on RCTs.

This systematic review included eight randomized controlled trials, among which six studies were eligible for a meta-analysis.

There was no statistically significant difference between the resorbable group and non-resorbable group with respect to CAL gain and pocket probing depth; however, a significant result was seen in gingival recession (at a 6-month interval) and intrabony defect depth (at all intervals and at a 6-month interval), favoring the resorbable membrane group. A subgroup analysis was carried out assessing the PPD at all intervals based on the study design. Astonishingly, it was found that the studies with split mouth design showed statistically significant effects, favoring the non-resorbable membrane. This could be due to the fact that split mouth RCTs are robust, and the effect could be exhibited in a similar oral environment without much bias in inter-patient variability and patient compliance.

The main advantage of a resorbable barrier membrane is that it does not require second surgical exposure for the removal of the membrane. Moreover, the tendency for membrane exposure and bacterial contamination are the problems commonly associated with a non-biodegradable membrane which might affect the defect fill. Among the included articles, two studies showed favorable results in terms of assessing gingival recession at a six-month interval [27,31]. The reason could be due to the need for removing the non-resorbable membrane, which will require a second surgical intervention. This could lead to progressive attachment loss and ultimately result in less recession coverage. Four included studies [27–29,32] showed significant results favoring the resorbable membrane in terms of intra-bony defect depth at all intervals (6–12 months) and at 12-month intervals [29,32].

Few studies have presented histological evidence of regeneration of bone through the use of lactic acid membrane and bovine bone matrix membrane respectively [33,34]. Moreover, one study did use an advanced imaging technique (CBCT) to estimate the quality and quantity of the newly formed bone via bone density and Hounsfield units, and these values suggested that collagen membranes were effective [35]. On the contrary, few studies have suggested that there is no statistically significant difference between collagen-covered defects and uncovered defects in terms of bone regeneration [36,37].

The results of this present study are in accordance with another study, which compared a non-resorbable GTR membrane with a conventional flap, in which there was no statistically significant difference in the test and control groups in terms of improvement of CAL and PPD [38]. When a resorbable polyglycolide membrane (RESOLUT XT) was used in aggressive periodontitis patients, an average ΔCAL of 3.4 [2.3] mm and an ΔPPD of 4.0 [2.1] mm at 12 months post-operatively were reported [39].

In contrast, a follow-up study carried out by Irokawa et al. resulted in significant improvement in the CAL and PPD gain in sites treated with resorbable membranes and deproteinized bovine bone material [40]. CAL gains at 1 and 2.5 years were significantly

reduced from that at 6 months. A significant improvement in PD was also noted: mean reductions in PD at 6 months and 2.5 years were 4.0 ± 0.8 and 3.2 ± 0.8 mm, respectively.

The defect fill in this systematic review is in correlation with the other studies by Garrett et al. [17] and Stavropoulos et al. [41]. This gain in the resolution of osseous defects is attributed to characteristics of the resorbable membrane such tissue integration, cell occlusivity, clinical manageability, space making, and biocompatibility.

The evaluation period of six months was frequently used because that is the most usual time frame in most clinical studies to evaluate the outcomes of regenerative periodontal surgery. In this systematic review, a time range of 6–12 months was preferred rather than a particular month. A subgroup analysis was performed based on the follow-up period. A subgroup analysis based on the type of membranes used was not possible because of a lack of studies which directly compared resorbable with non-resorbable membranes. The subgroup analysis of pocket probing depth shows a significant result ($p \leq 0.00001$) at all-time intervals (6–12 months) in the split mouth study group favoring the non-resorbable membrane group. A sensitivity analysis was carried out by removing studies lying outside the funnel plot (Figure A1 in Appendix A) to find no change in the effect estimate for all clinical parameters.

While treating advanced intra-bony periodontal defects, the GTR membrane along with grafting materials showed better outcomes. Yuan et al. [42] in 2021 treated the intrabony defects with GTR membrane (control group) and the GTR membrane along with grafting material (observational group). Six months after surgery, there was no significant difference in PLI and SBI scores between the two groups ($p \leq 0.05$). The gingival cosmetic scores of the two groups of patients were higher than those before surgery. The observation group was higher than the control group ($p \leq 0.05$). Another retrospective study by Artzi et al. [43] in 2015 evaluated the efficacy of the resorbable GTR membrane along with deproteinized bone xenografts and compared it with the combination of enamel matrix derivative and deproteinized bone xenografts in aggressive periodontitis patients. The authors of the abovementioned study found that both GTR and EMD groups of treatment resulted in successful clinical results after 1 year. Friedmann et al. [44] in 2020 also reintroduced polylactic acid (PLA) matrix barrier and evaluated the feasibility of the surgical approach. The authors recorded the change from grade II furcation to grade I, or complete resolution of the furcation involvement in 8 from 11 sites included, after a 12-month observational period [44].

In light of using periodontal regeneration in immunocompromised and systemic disorder patients, the progression of diabetes mellitus and the response to periodontal treatment such as GTR are affected by the patient's susceptibility to periodontal disease and delayed wound healing. Various mechanisms were involved for delayed wound healing, such as microvascular complications, impaired cell function, decreased tissue oxygenation, increased collagenase production, the deregulation of cytokines at the wound site and the decreased migration of periodontal ligament cells, which may affect the regeneration [45,46]. Therefore, patients with diabetes need close monitoring and frequent follow-ups of the GTR site to attain long-term success.

Guided tissue regenerative therapy is more effective in improving the periodontal treatment outcome compared to the open flap debridement procedure, including improved clinical attachment gain, the reduction in probing depth, and the gain in hard tissue. However, there are a few limitations in this systematic review as a result; it is difficult to draw general conclusions about the clinical benefit of resorbable GTR membrane. Although there is evidence that GTR therapy can lead to significant regeneration over conventional flap surgery, the factors affecting outcomes are unclear, and these might include study conduct issues such as bias. Factors such as the variability of the different types of membranes used, different types and configurations of intra-bony defects, host response of the patients, the various surgical procedures selected, and the different brands of biomaterials used can lead to bias. Therefore, both patients and health professionals need to give a thought to the predictability of the technique compared with other methods of treatment before making final

decisions on use. Since trial reports were often incomplete, we recommend that future trials should follow the CONSORT statement, both in their conduct and reporting. Moreover, no recently published clinical trials were included in this systematic review. Lastly, a subgroup analysis with types of bone defects, types of resorbable or non-resorbable membrane cannot be done because of the lack of studies.

5. Conclusions

Within the limitation of this systematic review, it was found that a resorbable membrane wields significant improvement in terms of gingival recession coverage and defect fill in the treatment of periodontal intra-bony defects. Therefore, it is quite reasonable to propose that resorbable membranes could be taken as a favorable treatment option, which will promote periodontal regeneration due to its proven biocompatibility, ease of handling, and no requirement of second surgical intervention. However, there are very limited studies available to compare these two types of treatment strategies. Recent advances in science and technology have led to the increased enthusiasm of approaches such as the electro-spinning of bio-mimetic and multifunctional membranes, nano-particle embedded polymeric membranes, etc. Therefore, it would be recommended to conduct future studies comparing different types of regenerative membranes in adjunct to different surgical techniques for the treatment of intra-bony defects.

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Abbreviations

RCT	Randomized controlled trial
PAL	Probing Attachment Level
CAF	Coronally Advanced Flap
PLA	Polyglycolide-co-Lactide
ePTFE	Expanded Polytetrafluoroethylene
GTR(R)	Resorbable Guided Tissue Regeneration Membrane
GTR(NR)	Non-Resorbable Guided Tissue Regeneration Membrane
GTR	Guided Tissue Regeneration
PPD	Probing Pocket Depth
CAL	Clinical Attachment Level
FMBS	Full Mouth Bleeding Score
GR	Gingival Recession
REC	Recession Coverage
PI	Plaque Index
GI	Gingival Index
BOP	Bleeding on Probing
NR	Not Reported
IBDF	Intrabony Defect Fill
PAL	Probing Attachment Level

PBL	Probing Bone Level
DFDBA	Demineralized Freeze Dried Bone Allograft
CS	Calcium Sulphate
BG	Bioactive Glass
NM	Non-resorbable Membrane
RM	Resorbable Membrane
OFD	Open Flap Debridement
ePTFE	Expanded Polytetrafluoroethylene
SD	Standard Deviation
MD	Mean Difference
MESH	Medical Subject Headings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis

Appendix A

Table A1 presents a list of the studies excluded from the review after reading their full texts.

Table A1. List of excluded studies after reading the full text.

Author and Year of Study	Reason of Exclusion
Górski et al., 2017 [38]	Compared two types of RB membrane
Kiany et al., 2015 [39]	Compared two types of RB membrane
Chung et al., 2014 [47]	Compared two types of RB membrane
Moder et al., 2012 [48]	Compared APC with GTR
Gamal et al., 2012 [49]	Compared two types of RB membrane
Budhiraja et al., 2012 [50]	Compared two types of RB membrane
Nygaard-Østby et al., 2010 [51]	ABG and GTR is compared with bone graft
Silvestri et al., 2010 [52]	Case series
Orsini et al., 2008 [53]	Compared bioresorbable membrane and bone graft with bone graft alone
Pretzl et al., 2008 [54]	Case series
Sculean et al., 2008 [55]	Compared EMD with RB membrane
Sculean et al., 2007 [56]	Compared GTR with OFD
Sipos et al., 2005 [57]	Combined use of EMP and barrier membrane
Stavropoulos et al., 2004 [41]	Case series
Joly et al., 2002 [58]	Compared resorbable membrane with open flap debridement
G.Zucchelli et al., 2002 [59]	Combined use of EMP and barrier membrane
Windisch et al., 2002 [9]	Compared GTR plus EMD with EMD alone
Lekovic et al., 2001 [60]	Compared RB with EMP and BPBM
Sculean et al., 2001 [61]	Compared NR membrane with NR plus EMD group
Christgau et al., 2001 [62]	Compared two types of RB membrane
Trejo et al., 2000 [63]	Compared bioresorbable barrier membranes with decalcified freeze dried bone allograft
Nickles et al., 2000 [64]	Compared RB with OFD
Dörfer et al., 2000 [65]	Compared two types of RB membrane

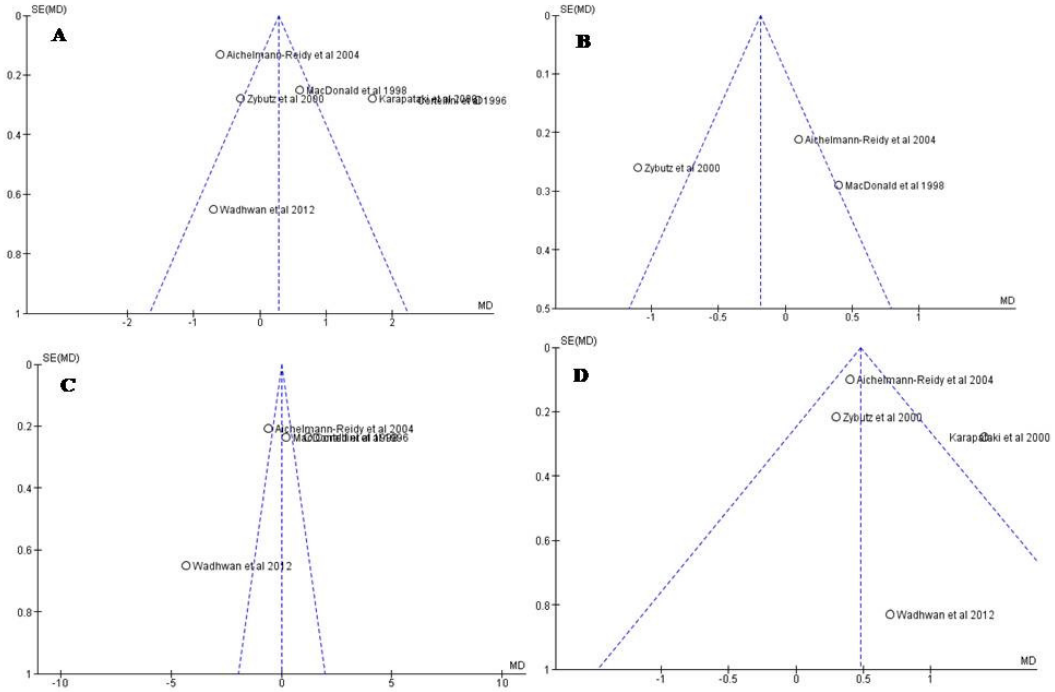

Figure A1. Funnel plots showing publication bias: (**A**) probing pocket depth; (**B**) clinical attach-ment level; (**C**) gingival recession; (**D**) intra bony defect depth.

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