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Systematic Review

Peri-Implantitis Therapy Using Surgical Methods: A Systematic Review

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Abstract: This study is a systematic review evaluating published literature on the effect of surgical treatments on peri-implantitis. Various databases were selected for the literature search on the topic. The considered primary clinical parameters were changes in probing pocket depth (PPD), bleeding on probing (BoP), radiographic bone change, plaque score, signs of infection, and implant loss. Five research studies comprising 20 or more sample sizes (patients) with minimal two-year follow-up after surgical treatment were selected, based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. In all five studies, PPD and BoP were significantly reduced compared to those before intervention. However, there was no significant variation in the patients treated with open flap debridement, citric acid decontamination, and subepithelial connective tissue graft. The highest reduction of BoP was recorded in the study utilizing regenerative surgical therapy, deproteinized bovine bone mineral containing 10% collagen, the derivative of enamel matrix, and doxycycline. According to the two–five-year follow-up of this systemic review, surgical treatment, including bone substitute material, showed clinical improvement in the reviewed studies, compared to that before intervention; however, there was no statistical significance in the clinical outcome of the selected studies.

Keywords: dental implants; implant; dentistry; implant survival; implantoplasty; peri-implant surgery; peri-implantitis; osteoplasty

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1. Introduction

Dental implants are one of the most prevalent efficacious prosthetic treatment procedures that replace missing teeth through technically advanced procedures [1]. In different clinical situations, dental implants have become indispensable, establishing therapy with success rates of 82.9% that has been recognized in a 16-year follow-up study [2]. However, implants can be rejected due to inflammation and biological complications, such as peri-implantitis, caused by oral microflora [3,4]. Peri-implantitis is a type of peri-implant disease relating to implant sites that could result in the loss of the implant [5,6]. Recent research indicates that 1 in 4 patients receiving implant therapy are likely to show signs of peri-implant disease with varying degrees of severity [7].

Peri-implantitis is a pathological response that occurs in tissues around implants and is associated with the peri-implant mucosa inflammation and progressive loss of supporting bone [8]. The disease involves the implant-surrounding hard and soft tissues in a progressive and irreversible manner and is associated with bone resorption, decreased osseointegration, enhanced pocket formation, and purulence [9]. The peri-implantitis diagnosis is based on the observation of bleeding on probing (BoP), loss of supporting bone, suppuration, deep probing pocket depth (PPD > 5 mm), and the presence of mucosal recession [10]. Patient susceptibility is one of the main patient factors identified in many longitudinal and cross-sectional studies that can affect the development and progression of the disease [10,11]. In this regard, various factors, such as periodontitis-associated tooth loss, can increase the risk of peri-implantitis and loss of peri-implant marginal bone [12].

Peri-implantitis can also be caused by several implant-related factors. Implant design and its surface features might also contribute to the progression of peri-implantitis [10]. Implants with very rough surfaces, such as some plasma-sprayed or hydroxyapatite-coated implants with arithmetic mean surface roughness (Sa) of >2 µg, can significantly increase the incidence of peri-implantitis [13–15]. Some implant technical problems, such as a fractured abutment screw, can cause soft tissue problems, such as a draining sinus [10]. Thus, to manage peri-implantitis, it must be diagnosed correctly. Also, peri-implant tissues must be systematically and regularly monitored to determine whether the peri-implant tissues are healthy or not and to evaluate the severity of the disease [10].

There are several treatment methods for peri-implantitis; however, the main strategies for the disease treatment are based on the treatments used for periodontal infections as microbial biofilm has a similar role in the development of both peri-implantitis and periodontitis [16]. The best strategy for the treatment of plaque-induced peri-implant inflammatory diseases is prevention as peri-implantitis does not cause a predictable response to treatment [9]. Some strategies to prevent implant-associated infection include (i) immobilizing antimicrobial peptides of the implant surface that kill bacteria directly on contact, and (ii) promoting the attachment of gingival epithelial cells to the surface of titanium implants through the surface coating of the implant by peptides, which can strongly bind to the cell surface receptors of human gingival epithelium cells [17]. The gingival epithelium cells work as a physical barrier and prevent bacterial colonization on the titanium implant surface [17]. The treatment of peri-implantitis is difficult, mainly due to the difficulty in the decontamination of the roughened and threaded surfaces of exposed implants [9]. For this reason, surgical treatment is required for peri-implantitis therapy.

Various therapeutic techniques mainly based on the treatments used for periodontitis teeth have been used for peri-implantitis therapy. One of these methods is surgical therapy, where a combination of non-surgical methods, such as laser therapy and drug therapy along with rejective and/or regenerative procedures, is used [3]. The basic principles of surgical therapy comprise the removal of the peri-implant osseous defect by ostectomy, osteoplasty, and decontamination of the implant surface [1]. Implantoplasty is also a surgical treatment in peri-implantitis, where the supracrestal implant surface is smoothened and polished [18]. Recent research reported by Serino and Turri [19] showed that surgical pocket elimination and recontouring of bone combined with plaque control prior- and post-surgery in patients with the active peri-implant disease, represented an effective treatment. Another surgical method is implantoplasty that proved to be effective as a surgical treatment method. Romeo et al. [20] compared the therapeutic effects of implantoplasty and peri-implant resective surgery only on the marginal implant bone loss through a three-year follow-up radiographic assessment. The results demonstrated that implantoplasty was a promising strategy for the treatment of peri-implant infections and peri-implantitis progression. The results also demonstrated that marginal implant bone loss significantly decreased after resective surgery with implantoplasty compared to that of resective therapy only. Smeets et al. [3] also demonstrated that resective surgical therapy could be a recommended therapy for peri-implantitis. Ostectomy and osteoplasty in combination with implantoplasty can also effectively reduce or even stop the progression of peri-implantitis. However, as this strategy is associated with increased postoperative recessions, it is not appropriate for every situation, particularly in highly aesthetic sensitive areas [3]. In addition, Heitz-Mayfield et al. [21] confirmed that the application of an anti-infective protocol, including surgical access, the decontamination of the implant surface, and systemic antimicrobials continued by a strict post-operative protocol could be effective in the peri-implantitis treatment. In this study, open flap debridement and the decontamination of implant surface in combination with adjunctive systemic amoxicillin and metronidazole were used for the treatment of moderate to advanced peri-implantitis. The regenerative approach is another effective surgical treatment technique that has been studied in recent literature [22], while resective surgical therapy might be useful in re-osseointegration in only minor superficial defects [3]. However, full regenerative and

re-osseointegration are required to achieve a functional and long-term survival implant with aesthetic outcome [3]. Various experimental research has been conducted according to the principles of guided bone regeneration (GBR) to assess the application effect of different grafting material and/or resorbable membranes. The results of animal studies performed by Hurzeler et al. [23] in dogs showed that the therapeutic outcomes between GBR and GBR ± graft combinations were not significantly different; therefore, GBR procedures seem to be a predictable treatment for the peri-implant defects induced by plaque infection.

Additionally, numerous studies [24,25] have considered the treatment of peri-implantitis in humans using regenerative approaches. The results of a retrospective study [26] demonstrated that the periodontal flap with osteoplasty (47%) and bone replacement materials (20%) were the most widely used operative intervention, respectively. The results of this study also indicated that the cumulative success rate for both procedures was 69%, which significantly decreased in patients due to various risk factors (e.g., smoking, periodontal disease, and poor oral hygiene). The efficacy of the peri-implantitis treatment was reduced by severe periodontitis, severe marginal implant bone loss, poor oral hygiene, and low compliance [26].

The research question that comes to mind is 'what is the most effective surgical treatment technique in eliminating peri-implantitis?' Researchers have different opinions on using surgical intervention; however, the best possible approach is not very clearly described. Most of the available research has been conducted in a short-term follow-up (less than one year) and with a small sample size. The present study aims to evaluate studies that followed up on the treatment outcomes of peri-implantitis for the long term and verified whether the association of surgical methods with other treatment options is beneficial. The first aspect of the study was to search the literature to understand the currently available surgical techniques to treat peri-implantitis. The second stream of literature focused on classifying the best possible treatment methods under different scenarios. We mapped the literature to understand the best possible surgical treatment technique for peri-implantitis and discuss future treatment possibilities.

Aim/Hypothesis: To evaluate the benefit of surgical treatment methods in the treatment of peri-implantitis and determine if there is any benefit when surgical methods become associated with other treatment options based on the studies considering the surgical treatment approaches for peri-implantitis, reported in the databases (PubMed, Scopus, and Web of Science) until 2023.

2. Materials and Methods

2.1. Protocol

The protocol of the study was designed based on the preferred reporting items for systematic review and meta-analysis (PRISMA) statement [27].

2.2. Focused Question

The focused question was performed based on the PICO format: in patients requiring peri-implantitis treatment, what benefit of surgical treatment methods alone and in combination with other treatment options could be expected?

The PICOs elements were as follows:

Population (P): Inclusion: Healthy patients, with at least one implant with BoP that needs peri-implantitis treatment with a clinical follow-up above two years post-operative.
Intervention (I): Peri-implantitis treatment performed with surgical therapy along with post-operative clinical evaluation.
Comparison (C): PPD and BoP, at the implant site, before and after (at least two years) treatment of peri-implantitis.
Outcome (O): Outcomes measuring changes in parameters, such as PPD and BoP.

2.3. Search Strategy

In this systematic review, a search strategy was used to identify relevant literature. First, an electronic literature search was performed in three databases—Scopus, PubMed, and Web of Science—and the keywords used were "surgical treatment peri-implantitis", or "peri-implantitis". All searches spanned from the database until 2023 and comprised journal articles, review papers, and research reports published in English only.

2.4. Selection Criteria

The selection criteria were made according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) quality assessment. All publications were carefully examined to keep the quality of the review, and those publications were selected that considered adult subjects with good general health, at least a two-year follow-up period, and where the number of implants reviewed was not less than 20. Furthermore, studies were selected that assessed the effectiveness of therapies by comparing the changes in clinical parameters, including a reduction in PPD and BoP. This study was based only on original research, review, and conference articles [28].

2.5. Study Selection

Two independent reviewers (SW and AS) performed electronic and manual literature searches and chose eligible studies by analyzing the titles list and abstracts and regarding the inclusion and exclusion criteria. Those articles with eligible titles and abstracts were independently examined to determine eligibility. Disagreements between the reviewers relative to choosing and inclusion of any article were discussed to reach a consensus, and if no agreement was reached, the third and fourth reviewers (SEA and LAS) determined the inclusion or exclusion.

2.6. Study Quality Assessment

The risk of bias was assessed by two authors (SW and AS), and disagreements were resolved via consensus with the third and fourth reviewers (SEA and LAS). The individual risk of bias in all randomized clinical trials (RCTs) was assessed using RoB 2, based on the recommended Cochrane guidelines [29]. According to the RoB 2 tool, the risk of bias was considered for each outcome as: (i) low if sufficient information was available; (ii) moderate if there was no sufficient information, and the risk of bias was impossible to be determined; and (iii) high if no information was available. Also, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was utilized to measure the bias of each non-RCT's outcome and considered as low, moderate, and serious [30].

2.7. Data Analyses

Descriptive statistics were utilized to show the primary result in terms of PPD and BoP reduction, and $p < 0.05$ was considered significant.

3. Results

3.1. Study Selection

The processes of search and selection are described in Figure 1. As the figure shows, from 1986 included studies, 1397 studies were removed as duplicate studies. From the remaining studies, 573 studies were also removed as these studies did not meet the selected criteria, and 16 articles were selected for retrieval. From these retrieved studies, 11 studies were excluded because they did not follow up on the treatment outcomes for two years and more, and the number of implants reviewed was lower than 20. Thus, 5 studies were selected for this systemic review.

3.2. Study Characteristics

The characteristics of the research articles included are displayed in Table 1. Table 2 shows the results summary of the five studies. The total number of patients treated in these

studies was 154. The follow-up period was two–five years. One study [25] compared the effectiveness of the addition of bone substitute material with (group 1) or without membrane (group 2) after surgical debridement. The results of the five-year follow-up demonstrated that both clinical and radiographic were improved. Moreover, no implants were lost owing to peri-implantitis progression. PPD was reduced by 3.0 ± 2.4 mm and 3.3 ± 2.09 in groups 1 and 2, respectively. Both groups demonstrated significant radiographic evidence of bone gain ($p < 0.001$). The average defect fill measured by an oral radiologist at year 5 was 1.3 mm (SD 1.4 mm) and 1.1 mm (SD 1.2 mm) in groups 1 and 2, respectively (mean diff; 0.4 95% CI 0.3, 1.2, $p = 0.24$). Both groups demonstrated a decrease in BoP. At baseline, the suppuration occurred in 19.9% and 22.7% of implants in groups 1 and 2, respectively, while at five years post-surgery, the implants in both groups did not show suppuration. According to the results of this study [25], both therapeutic approaches caused stable conditions. In addition, it was found that the use of a membrane does not improve the outcome. A similar study performed by Mercado et al. [31] used deproteinized bovine bone mineral containing 10% collagen (DBBMC) combined with enamel matrix derivative (EMD) and doxycycline powder in the regeneration of bone defects due to peri-implantitis. The results demonstrated that while the mean PPD and bone loss at the baseline were 8.9 ± 1.9 mm and 6.92 ±1.26 mm, respectively, these values were reduced significantly to 3.55 ± 0.50 mm and 2.85 ± 0.73 mm at 12 months, 3.50 ± 0.50 and 2.62 ± 0.80 mm at 24 months, and 3.50 ± 0.50 mm and 2.60 ± 0.73 mm at 36 months, respectively. In addition, it was found that 56.6% of the implants were successfully treated after 36 months. According to the results of this study, using a mixture of DBBMC, EMD, and doxycycline is a promising approach for the regenerative treatment of peri-implantitis. Dalago et al. [32] compared various combinations of open flap debridement (OFD), citric acid decontamination (CAD), subepithelial connective tissue graft (SCTG), and implantoplasty to determine the most effective treatment combination. They divided patients into three groups and the groups received the treatments as follow: group 1: OFD and CAD; group 2: OFD, CAD, and SCTG; and group 3: OFD, CAD, and implantoplasty. The results demonstrated that all therapies (OFD, CAD, SCTG, and implantoplasty) were effective in managing peri-implantitis in 50%, 60%, and 62.5% of implants for groups 1, 2, and 3, respectively, with 91.30% overall survival rate of the implant after three-year follow-up; however, SCTG caused the highest keratinized mucosa width by ~42.7%. Furthermore, the results demonstrated that the treatment modalities were all effective in decreasing the progression of crestal bone loss by ~8.9% in groups 1 and 2, respectively, and by ~13.5% in group 3. According to the results of this study [32], all therapies were found effective for the treatment of peri-implantitis; however, SCTG demonstrated the highest efficacy in achieving the biggest keratinized mucosa width. Overall, a combination of surgical therapies with mechanical and chemical decontamination could be efficient in treating peri-implantitis [32]. Moreover, the effectiveness of osteoplasty, implantoplasty, and the apically positioned flap was investigated by Englezos et al. [33]. The results of this study [33] demonstrated that after two years, no implants were lost and the mean PPD decreased from 8.7 to 3.3 mm, and the stability of bone level was kept in 92.5% of the implants. Also, at the final period of assessment, plaque was observed in 32.5% of patients. Moreover, while BoP was observed in all implants at baseline, this parameter was observed only in 10 of 40 implants two years after therapy. Furthermore, at baseline, suppuration was observed in 70% of implants, while this value, two years post-therapy, was 2.5%. Finally, the results of this study suggest that using a combination of the apically positioned flap, osteoplasty, and implantoplasty is a promising approach for the peri-implantitis treatment; however, increased gingival recessions can be a limitation to restrict its use in aesthetic areas. Isler et al. [34] used two different reconstructive surgical treatments of peri-implantitis including a xenogenic bone grafting material combined with either concentrated growth factor (CGF; group 1) or collagen membrane (CM; group 2) and compared the three-year clinical and radiographic outcomes. Both approaches were found effective in treating peri-implantitis; however, using CM, compared to CGF, was found to be more efficient in improving the peri-implantitis treatment outcome

in terms of PPD, RBG, plaque score, and BoP [34]. In addition to surgical therapies, patients in Englezos et al. [33], Mercado et al. [31], Roos-Jansåker et al. [25], and Isler et al. [34] were prescribed antibiotics and analgesics.

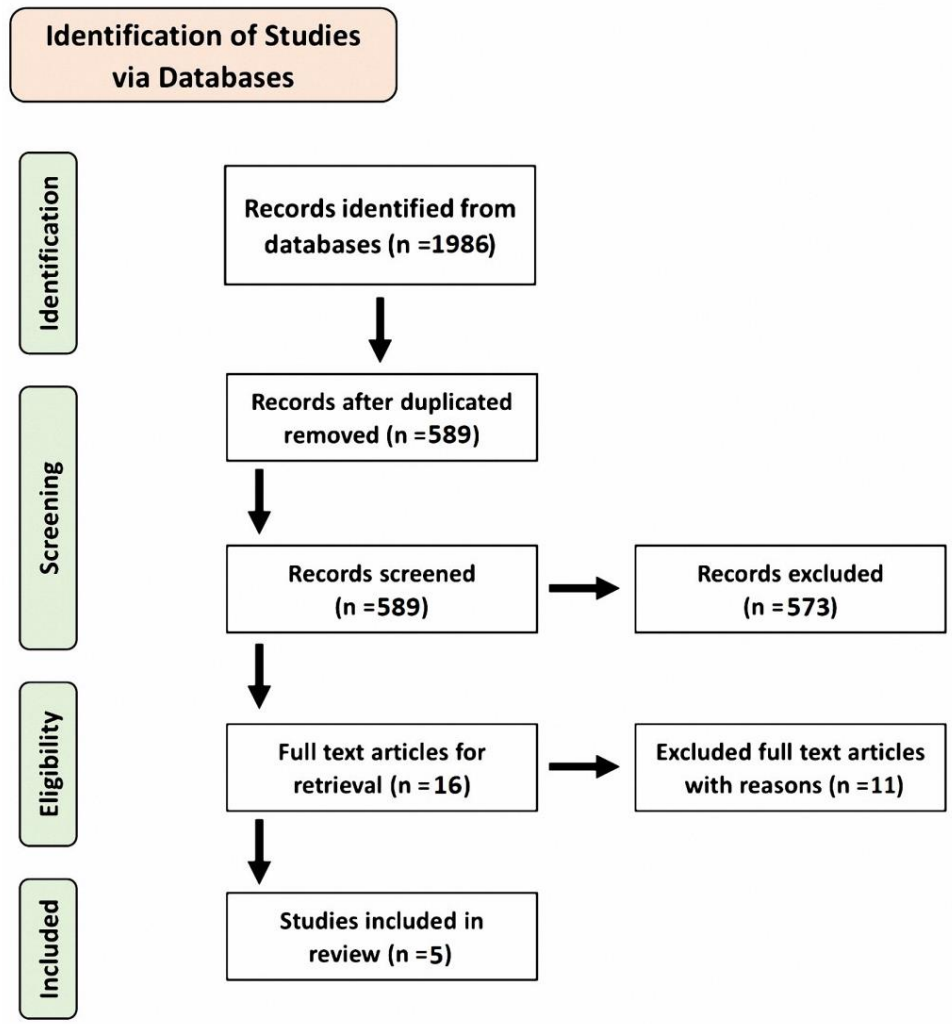

Figure 1. Illustration of the review process based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA). As the Figure shows, overall, 1986 studies were included, and after removing the duplicate studies, 589 remained. At this stage, all the irrelevant studies were removed as these studies did not consider adult subjects with good general health or did not consider the intended clinical parameters, and 16 articles were selected for retrieval. From these articles, 11 articles were excluded because they followed up on the treatment outcomes for less than two years, and the number of implants reviewed was less than 20. Therefore, 5 studies were selected for this systemic review.

Table 1. Properties of the studies used in the present systematic review.

Study	**[25]**	**[31]**	**[32]**	**[33]**	**[34]**
Study design	Randomized controlled clinical trial	Randomized clinical trial	Longitudinal comparison	Randomized clinical trial	Randomized clinical trial
Sample size	25 patients 45 implants	30 patients 30 implants	23 patients 23 implants	25 patients 40 implants	51 patients 52 implants
Follow-up duration (year)	5	3	3	2	3

Table 1. *Cont.*

Study	[25]	[31]	[32]	[33]	[34]
Mean age of the patient (year)	Not stated	44.9 ± 11	50–52	66.2	57
Gender	Not stated	Not stated	6 men 17 females	8 men 17 females	27 men 24 females
Inclusion criteria	PPD ≥ 1.8 mm, BoP, horizontal and vertical crater-like bone loss.	Systemically healthy, non-smokers, full mouth bleeding score below 20%, 1 implant infected, crater-like or circumferential bone loss, PPD ≥ 4 mm, 20% loss of crestal bone, for at least 2 years in function.	PPD ≥ 5 mm BoP, crestal bone level > 2 mm.	PPD ≥ 6 mm, BoP at the affected implant, radiographic evidence of bone loss ≥ 3 mm.	having at least one implant showing two-, three-, or four-wall infrabony defects ≥ 3 mm, presenting a PPD of ≥5 mm with BoP and/or suppuration.
Exclusion criteria	Radiographic evidence of horizontal bone loss only and without evidence of a vertical crater-like defect.	Uncontrolled diabetics, taking bisphosphonates, pregnant and lactating females.	Peri-implant graftable defects, smoking habits, diabetics type 1 and 11.	Implants with machined titanium surface, implants with clinically visible mobility, severe systemic disease patients.	Existence of severe systemic diseases, medications, or conditions that inhibited periodontal surgery and would jeopardize wound healing; using systemic antibiotics during the past 3 months; placement and prosthetic loading of implants within the past year; and the existence of one-wall peri-implant intrabony defects.
Surgical treatment	Full-thickness flap, and removal of granulation tissue, implant surface debrided, treated with hydrogen peroxide (3%), and rinsed with saline, two groups, group 1 treated with the bone substitute with membrane, group 2 bone substitute alone. All participants received antibiotic coverage (amoxicillin 375 mg × 3 per day, and metronidazole 400 mg × 2 per day) at the first 10 days post-surgery.	Intra sulcular incision and the flap were extended, granulation tissue was removed, exposed implant thread was debrided using a fine tip low-power ultrasonic scaler, the mixture of deproteinized bovine bone mineral containing 10% collagen (DBBMC) + enamel matrix derivatives (EMD) applied to exposed threads and closure with coronally advanced flap. Connective tissue graft was done if there was 1 mm of keratinized gingiva in aesthetic zones or if the defect was in the aesthetic zone (anterior maxilla).	Raising full thickness mucoperiosteal flap, removing the granulation tissue, the implants' surfaces debrided, treatment in three groups. Group 1: chemical decontamination with 50% citric acid for 3 min Group 2: chemical decontamination with citric acid and the removal of subepithelial connective tissue graft (SCTG) from the palate and sutured over the exposed implant surface. Group 3: implantoplasty and chemical decontamination with citric acid.	Full thickness mucoperiosteal flap, pocket epithelium and granulation tissue removed, osteoplasty, implantoplasty, cleaning the implants using a gauze embedded in chlorhexidine and saline, irrigating the surgical site with saline to remove titanium particles from the surrounding tissues, apically positioned flap.	Producing sulcular incisions around the implants' neck and raising full-thickness mucoperiosteal flaps at the buccal and lingual aspects. Removing inflammatory tissues from the defects. Irrigating the surfaces with saline solution and then filling the intrabony defects by a xenogenic particulate graft material, two groups. Group 1: two pieces of concentrated growth factor (CGF) membranes were placed over the graft material. Group 2: covering the graft material with a bioresorbable collagen membrane (CM).

Table 1. *Cont.*

Study	[25]	[31]	[32]	[33]	[34]
Antibiotics	Amoxicillin 375 mg/day, Metronidazole 400 mg × 2/day during first 10 days following surgery	Doxycycline 100 mg was added to the bone substitute mixture	N/A	3 g amoxicillin per day for 1 week 0.12% chlorhexidine mouthwash for 1 week	Amoxicillin and metronidazole (500 mg) three times a day for 1 week after the surgery
Analgesics	Ibuprofen 400 mg × 3 days	Paracetamol 500 mg and Ibuprofen 150 mg	N/A	Ibuprofen and paracetamol	Flurbiprofen (100 mg, twice a day) in the first 3 days after the surgery
Follow-up	Every 3 months	Supportive periodontal therapy (SPT) was done 3, 6, and 12 months, and then every 4 months	6 months interval for plaque control, and then yearly clinical and radiographically exam for 3 years	1–3 months after therapy, 2–4 times per year for 2 years	Every third month from 6 to 36 months after the reconstructive surgical treatments

Table 2. A summary outcome and main findings of the included studies.

Study	[25]	[31]	[32]	[33]	[34]
Probing pocket depth (PPD)	Decreased compared to that of baseline in groups 1 (Bone substitute + membrane) and 2 (Bone substitute) by ~46.4% and 45%, respectively, at the final period of review.	Decreased compared to that of baseline by ~60.7% at the final period of review.	Decreased compared to that of baseline in groups 1 (chemical decontamination with 50% citric acid), 2 (chemical decontamination with citric acid and subsequent subepithelial connective tissue graft (SCTG)), and 3 (implantoplasty and chemical decontamination with citric acid) by ~24.2%, ~33%, and ~35.3%, respectively, at the final period of review.	Decreased compared to that of baseline by ~37.9% at the final period of review.	Decreased compared to that of baseline in groups 1 (two pieces of concentrated growth factor (CGF) membranes) and 2 (covering the graft material with a bioresorbable collagen membrane (CM)) by ~38.5% and ~53.6%, respectively, at the final period of review.
BoP mean	Decreased compared to that of baseline in both groups 1 and 2 by 100% at the final period of review.	Decreased compared to that of baseline by 80% at the final period of review.	Decreased compared to that of baseline in groups 1, 2, and 3 by 72.2%, 26.1%, and ~20%, respectively, at the final period of review.	Decreased compared to that of baseline by 75% at the final period of review.	Decreased compared to that of baseline in groups 1 and 2 by ~58.4% and ~63.4%, respectively, at the final period of review.
Radiographic bone gain (RBG)	RBG by 67.4% and 72.5% in groups 1 and 2, respectively, compared to that of baseline at the final period of the review.	RBG by 62.4% compared to that of baseline at the final period of review.	RBG by ~9%, 8.9%, 13.5% in groups 1, 2, and 3, respectively, compared to that of baseline at the final period of review.	RBG by ~3.8% compared to that of baseline at the final period of review.	RBG by 32.7% and 45.6% in groups 1 and 2, respectively, compared to that of baseline at the final period of the review.
Number of implant loss	No implants were lost.	No implants were lost.	11.1%, 16.7%, and 0% implants were lost in groups 1, 2, and 3, respectively, at the final period of the review.	No implants were lost.	No implants were lost.

Table 2. *Cont.*

Study	[25]	[31]	[32]	[33]	[34]
Plaque score	Decreased plaque score by 70% compared to that of baseline at the final period of review.	No change in plaque score compared to that of baseline at the final period of review.	Decreased plaque score by 43.6%, 20%, and ~38.7%, compared to that of baseline in groups 1, 2, and 3, respectively, at the final period of review.	Decreased plaque score by 67.5% compared to that of baseline at the final period of review.	Decreased plaque score by ~38.5% and ~53.6%, compared to that of baseline in groups 1 and 2, respectively, at the final period of review.
Suppuration	Decrease of suppuration occurrence compared to that of baseline by 19.9% and 22.7% in groups 1 and 2, respectively, at the final period of the review.	Decrease of suppuration occurrence compared to that of baseline by 80 at the final period of review.	Decrease of suppuration occurrence compared to that of baseline by 26.1%, 20%, and 72.2% in groups 1, 2, and 3, respectively, at the final period of review.	Decrease of suppuration occurrence compared to that of baseline by 96.4% at the final period of review.	N/A
Main result	Surgical treatment using a bone substitute at implants with intraosseous lesions could be a viable option. Using membrane did not improve the outcome.	Using DBBMC and EMD in combination with doxycycline was found to be effective in the regenerative therapy of peri-implantitis.	All therapies were effective for the management of peri-implantitis, but SCTG maintained the greatest keratinized mucosa width. Surgical therapies and mechanical and chemical decontamination were highly effective.	Apically positioned flap combined with osteoplasty and implantoplasty were found to be an effective and reliable strategy for the treatment of peri-implantitis but increased gingival recession in aesthetic areas.	Group 1, compared to group 2, could result in a slightly better outcome in reconstructive surgical therapy of peri-implantitis.

3.3. Study Quality Assessment

All RCTs studies demonstrated a low risk of bias for all RoB 2 domains, based on each outcome (Table 3). Furthermore, the risk of bias of non-RCTs, based on each outcome, was considered as low on the overall bias of the ROBINS-I tool (Table 4).

Table 3. Risk of bias of included RCTs studies using the RoB 2 tool. Green, yellow, and red are low, moderate, and high risk, respectively.

	Randomization Process	Deviations from Intended Interventions	Missing Outcome Date	Measurement of the Outcome	Selection of the Reported Result	Overall	Ref
PPD							[32]
BoP							
Plaque score							
RBG							
PPD							[34]
BoP							
Plaque score							
RBG							

3.4. Effect of Intervention on Probing Pocket Depth

PPD was measured in all the interventions in periodic examinations during the study period. The results demonstrated that PPD significantly decreased, compared to that of baseline, by ~44.8%, ~60.7%, ~30.8%, ~37.9%, and 37.5% in the Roos-Jansåker et al. [25], Mercado et al. [31], Dalago et al. [32], Englezos et al. [33], and Isler et al. [34] studies, respectively (Figure 2). The results of the Roos-Jansåker et al. study [25] demonstrated

that PPD decreased in both groups 1 (bone substitute material + membrane) and 2 (bone substitute material), in which PPD in group 1 decreased by 44.6 and 46.4% after one- and five-year treatments, respectively, while in group 2, these values were 43.3 and 45%, respectively. Mercado et al. [31] demonstrated that the mean PPD values decreased by 60.1% after one-year treatment, while this value after two- and three-year treatments was 60.7%. The difference in the PPD from pretreatment to one, two, and three years after treatment was statistically significant ($p < 0.01$). Englezos et al. [33] demonstrated that the difference in PPD prior- and post-treatment was statistically significant ($p \leq 0.001$). The highest mean reduction of PPD was found to be 5.4 mm. The surgical procedure in this study was pocket epithelium and granulation tissue removal, osteoplasty, implantoplasty, and apically positioned flap. Dalago et al. [32] reported that the lowest mean reduction of PPD was 1.87 mm in peri-implantitis patients treated with a combination of treatments, including OFD, CAD, and SCTG [32]. Also, Isler et al. [34] demonstrated that using the combination of CM + bone substitute, compared to CGF + bone substitute, was more efficient in decreasing PPD values by 25.9% and 9.6%, respectively; however, both treatment modalities were found to be efficient in decreasing the PPD values, in which PPD in group 1 decreased by 37.1% and 35.6% at year one and year three post-surgery, respectively, while these values for group 2 were 50.1% and 39.4%, respectively ($p < 0.05$) [34].

Table 4. Risk of bias of included non-RCTs studies using the RoB 2 tool. Green, yellow, and red are low, moderate, and high risk, respectively.

	Confounding	Selection of Participants	Classification of Interventions	Deviations from Intended Interventions	Missing Date	Measurement of the Outcome	Selection of the Reported Result	Overall Bias	Ref
PPD									[25]
BoP									
Plaque score									
RBG									
PPD									[31]
BoP									
Plaque score									
RBG									
PPD									[33]
BoP									
Plaque score									
RBG									

3.5. Effect of Interventions on Bleeding on Probing

BoP showed a significant reduction in all studies by ~86.1%, 80%, ~39.4%, 75%, and 60.9% in the Roos-Jansåker et al. [25], Mercado et al. [31], Dalago et al. [32], Englezos et al. [33], and Isler et al. [34] studies, respectively (Figure 3). In the Dalago et al. study [32], BoP at the final period of review, compared to that of baseline, decreased by 72.2%, 26.1%, and ~20% in groups 1, 2, and 3, respectively. The highest reduction in BoP was observed in the Roos-Jansåker et al. [25] study, in which bone substitute material and a resorbable membrane were used as a therapeutic approach. The results of the Mercado et al. study [31] demonstrated that while 100% of the treated implants had BoP at the baseline, this value decreased to 20% at years two and three after surgical treatment. Also, in the Englezos et al. study [33], all implants showed BoP at baseline; however, two years after surgical intervention only 10 of 40 implants (25%) demonstrated BoP. Moreover, the results of Isler et al. study [34] demonstrated that the application of a xenogenic bone grafting material with CGF or CM was efficient in treating peri-implantitis, where us-

ing these materials could decrease BoP values compared to the baseline by 66.35% and 60.9% at one and three years after surgical therapy, respectively; however, using the bone substitute + CM (group 2) was found to be more efficient, compared to the bone substitute + CGF (group 1), in decreasing the BoP values, in which the BoP values for group 1 decreased by 63.4% and 58.4%, at year one and year three after surgical treatment, respectively, while these values for group 2 were 69.3% and 63.4%, respectively.

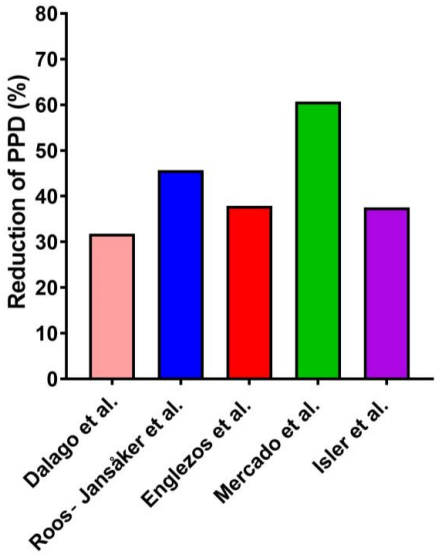

Figure 2. Reduction of PPD values after follow-up (i.e., after surgical treatment) compared to that of the baseline, reported by Dalago et al. [32], Roos-Jansåker et al. [25], Englezos et al. [33], Mercado et al. [31], and Isler et al. [34]. As these studies showed, the highest and lowest reductions were observed in the Dalago et al. and Mercado et al. studies, respectively.

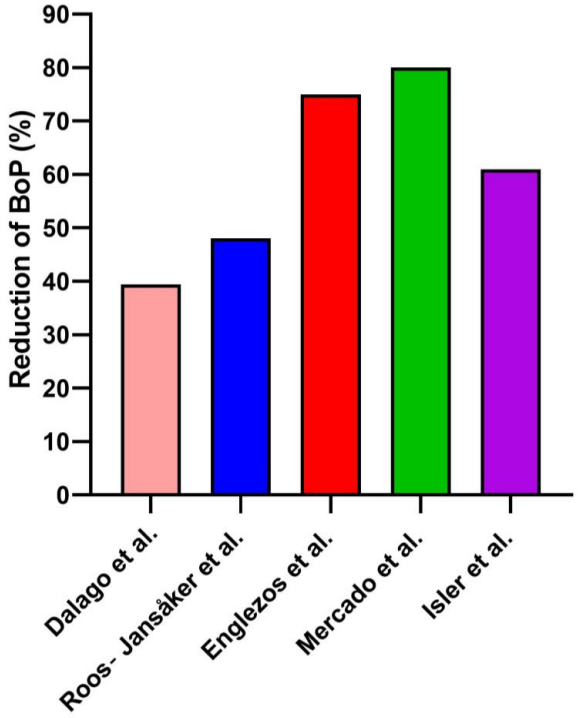

Figure 3. Reduction of BoP values after follow-up (i.e., after surgical treatment) compared to that of the baseline (before surgical treatment), reported by Dalago et al. [32], Roos-Jansåker et al. [25], Englezos et al. [33], Mercado et al. [31], and Isler et al. [34]. As these studies showed, the highest and lowest reductions were observed in the Mercado et al. and Dalago et al. studies, respectively.

3.6. Effect of Interventions on Radiographic Bone Gain

RBG in the Roos-Jansåker et al. study [25], between baseline and five years after treatment in groups 1 (bone substitute material + membrane) and 2 (bone substitute material) was 1.3 ± 1.2 and 1.1 ± 1.2 mm, respectively, that was equal to 67.4% and 72.5% RBG in groups 1 and 2, respectively. The results of the Mercado et al. study [31] demonstrated that the mean bone loss at the initial visit was 6.92 ± 1.26 mm, while this value at 12, 24, and 36 months after treatment was 2.85 ± 0.73, 2.62 ± 0.80, and 2.60 ± 0.73 mm, respectively, demonstrating that the treatment caused a significant decrease in the mean bone loss ($p > 0.01$). In other words, RBG three years after treatment, compared to that of baseline, occurred by 62.4%. Dalago et al. [32] demonstrated that the crestal bone level in groups 1, 2, and 3 at the baseline was 4.98 ± 0.42, 4.32 ± 0.74, and 5.53 ± 0.57 mm, respectively, while these values three years after treatment were 5.47 ± 0.63, 4.74 ± 0.90, and 6.39 ± 0.58, respectively, indicating bone gain that was higher in group 3 compared with groups 1 and 2. Also, the results of the Englezos et al. study [33] demonstrated that marginal bone level prior to and two years after treatment were 5.1 and 5.3 mm, respectively, indicating bone gain by ~3.8%. In addition, Isler et al. [34] demonstrated that the treatment regimen containing a xenogenic bone grafting material combined with either CGF or CM could increase RBG compared to that of baseline by 39.2% at year three after surgery. Also, the results demonstrated that the treatment regimen in group 2 (bone substitute + CM), compared to that of group 1 (bone substitute + CGF), was more efficient in increasing bone gain by 39.9% and 28.3% at years one and three post-surgery, respectively, indicating the higher efficacy of bone substitute + CM, compared to bone substitute + CGF, in the bone regeneration (Figure 4).

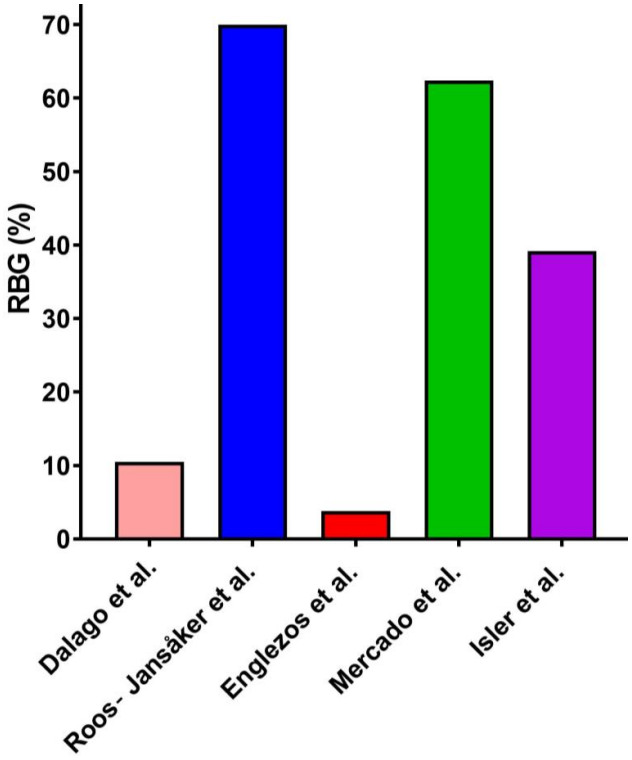

Figure 4. Radiographic bone gain (RBG) values after follow-up (i.e., after surgical treatment) compared to that of the baseline (before surgical treatment), reported by Dalago et al. [32], Roos-Jansåker et al. [25], Englezos et al. [33], Mercado et al. [31], and Isler et al. [34]. As these studies showed, the highest and lowest RBG values were observed in the Roos-Jansåker et al. and Englezos et al. studies, respectively.

3.7. Effect of Interventions on Plaque Score

The plaque score in the Roos-Jansåker et al. study [25] decreased by 70% after five-year treatment, compared to that of baseline, while in the Dalago et al. study [32], the plaque score decreased by ~34.1% after three years of treatment. Also, the results of the Mercado et al. study [31] demonstrated that plaque score was less than 20% at every review visit, while the results of the Englezos et al. study [33] demonstrated that the plaque score decreased by 67.5% at the final period of review, compared to that of baseline. In addition, the results of the Isler et al. study [34] showed that the application of a combination of xenogenic bone grafting material with either CGF or CM was efficient in decreasing the plaque score by ~46.1% at three years after surgery compared to that of baseline (Figure 5).

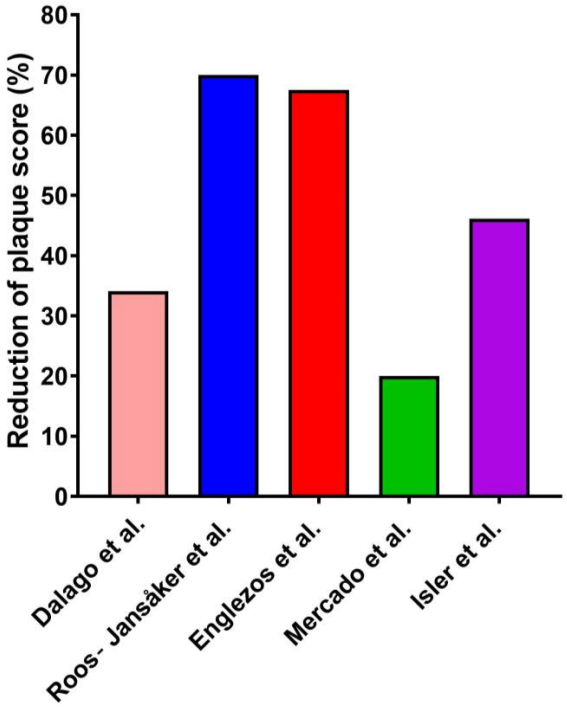

Figure 5. Reduction of plaque score values after follow-up (i.e., after surgical treatment) compared to that of the baseline (before surgical treatment), reported by Dalago et al. [32], Roos-Jansåker et al. [25], Englezos et al. [33], Mercado et al. [31], and Isler et al. [34]. As these studies showed, the highest and lowest reductions were observed in the Roos-Jansåker et al. and Mercado et al. studies, respectively.

3.8. Effect of Interventions on Suppuration

The results of the Roos-Jansåker et al. study [25] demonstrated that suppuration at baseline occurred at 19.9% and 22.7%% of implants in groups 1 and 2, respectively, while five years after treatment no suppuration was observed in implants. The results of the Mercado et al. study [31] showed that applying four-monthly supportive periodontal therapy (SPT), compared to six-monthly SPT, caused a 60% decrease in the rate of suppuration. In this study [31], the suppuration rate decreased by 80% at the final period of review compared to that of the baseline. In the Dalago et al. study [32], the highest decrease in suppuration was observed in group 3, in which suppuration decreased by 72.2% at three years, compared to the baseline. This value in groups 1 and 2 decreased by 26.1% and 20%, respectively. In addition, the Englezos et al. study [33] demonstrated that the rate of suppuration significantly decreased two years after surgical therapy, compared to that of baseline, in which, while at the baseline suppuration occurred in 70% of implants, this value two years after treatment decreased to 2.5%. In other words, the suppuration rate decreased by 96.4% in the final period of review compared to that of the baseline.

3.9. Effect of Interventions on Implant Loss

The results of the Roos-Jansåker et al. study [25], the Mercado et al. study [31], the Englezos et al. study [33], and the Isler et al. study [34] demonstrated that no implants were lost during the five, three, two, and three years after treatment, respectively. In addition, in the Dalago et al. study [32], the overall implant survival rate was found to be 91.30% during three-year follow-up, in which 88.89%, 83.33%, and 100% of implants in groups 1, 2, and 3, respectively, were functioning during this time (Figure 6).

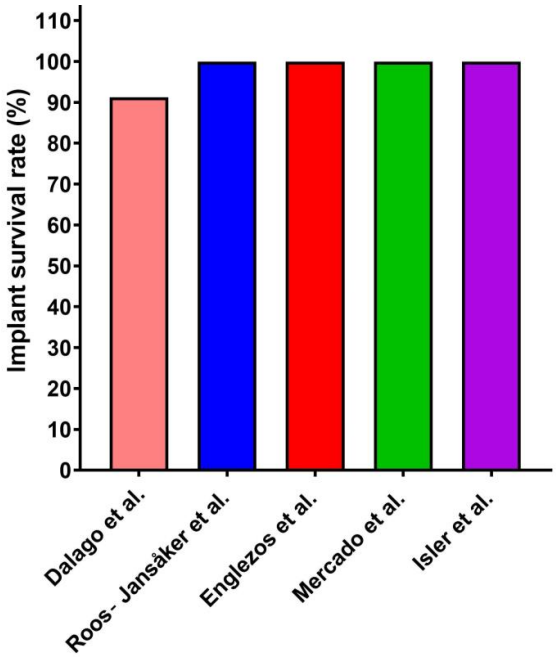

Figure 6. Values of implant survival rate after follow-up (i.e., after surgical treatment) compared to that of baseline (before surgical treatment), reported by Dalago et al. [32], Roos-Jansåker et al. [25], Englezos et al. [33], Mercado et al. [31], and Isler et al. [34]. As these studies showed, only in the Dalago et al. study the survival rate was below 100%, while in other studies this value was 100%.

4. Discussion

Regarding the clinical parameters, all five studies demonstrated an improvement in the clinical condition after the treatment, i.e., the clinical parameters, such as PPD and BoP, decreased by 42.7% and 60.7%, respectively, in the studies at the end of follow-up compared to those of baseline. The highest reduction in PPD was reported by Mercado et al. [31], Roos-Jansåker et al. [25], Englezos et al. [33], Isler et al. [34], and Dalago et al. [32], by 60.7%, 44.8%, 37.9%, 37.5%, and 30.8%, respectively. Englezos et al. [33] used osteoplasty, implantoplasty, and apically positioned flap for surgical treatment, while Mercado et al. [31], Roos-Jansåker et al. [25], and Isler et al. [34] used bone substitute material and regenerative techniques. This could indicate that regenerative techniques might be as effective as surgical methods alone. Reduction in PPD along with RBG in the Mercado et al. study [31] demonstrated that using a combination of DBBMC, EMD, and doxycycline powder is effective as a therapeutic approach for regenerative therapy of peri-implantitis. The results of the Dalago et al. study [32] demonstrated that when chemical decontamination was used with implantoplasty in group 3, PPD, BoP, and suppuration significantly decreased. Also, using SCTG in group 2 was found to be effective in thickening the peri-implant keratinized tissue [32]. It has been demonstrated that the grafting of connective tissue (keratinized tissues) to cap implants influenced by peri-implantitis improves peri-implant health [32]. Moreover, the band of keratinized tissue in peri-implant can improve oral hygiene and preclude larger tissue damage owing to the difficulty in the control of plaque in the areas, which have the least keratinized mucosa. Nonetheless, the keratinized mucosa dimension can be a risk factor that increases the likelihood of peri-implantitis occurring [32]. The

ideal treatment of peri-implantitis is the full resolution of the disease and reorganization and preservation of healthy peri-implant tissues. It can be clinically achieved when peri-implant PPD is less than 5 mm, with no BoP, no suppuration, and no ongoing loss. As this condition is rarely reported in the literature, the proposed criteria for successful treatment of the disease is implant survival, mean PPD less than 5 mm, and no ongoing loss. In the Englezos et al. study [33], no implants were lost, and 92.5% of implants had the aforementioned criteria. However, when BoP was added to the criteria, the treatment success rate decreased to 75%. Also, the results of this study [33] demonstrated that plaque control was a critical factor in the peri-implantitis treatment, in which all implants which had low plaque scores remained stable, while two patients who had implants with high plaque scores demonstrated progressive bone loss. Overall, the results of this study demonstrated that surgical therapy to eliminate pockets along with apically positioned flap, osteoplasty, and implant surface smoothing could be considered a promising therapeutic approach for stopping the progression of peri-implantitis; however, controlling the plaque is of great importance. Also, the aesthetic outcome can limit the applicability of this therapeutic approach in the anterior maxilla [33]. The results of the Isler et al. study [34] demonstrated that 26.9% and 34.6% of patients in group 1 and group 2, respectively, had no additional bone loss, no BoP or suppuration with a maximum PPD of $\leq$5 mm, at year three after surgical treatment, indicating the higher therapeutic efficacy of bone substitute + CM, compared to that of bone substitute + CGF, in the treatment of peri-implantitis. Also, the results of this study demonstrated that prognostic indicators, such as history of periodontitis, radiographic vertical defect depth (VDD) at the baseline, and the configurations of peri-implant bone defect, negatively affected the treatment outcome, in which patients with a history of periodontitis and higher VDD values had poorer treatment outcome. Moreover, patients with four-wall defects, compared to those with other defect types, have more favorable treatment outcome. The long-term (five years) effects of regenerative treatment on peri-implantitis were evaluated by Roos-Jansåker et al. [25]. In this study, the highest reduction of BoP was observed by ~86.1% using bone substitute material and a resorbable membrane. After surgical intervention, all individuals in the study utilized supportive therapy, including oral hygiene, and the plaque was controlled very efficiently throughout the study. Perfect oral health is a prerequisite for the successful treatment of implants. The authors [25] demonstrated that using the resorbable membrane to cover the bone substitute had no improvement effects on the long-term outcomes. Moreover, in this study patients were not randomly assigned to treatment groups; thus, further research studies are needed and should further assess various surgical therapeutic approaches using a randomized clinical trial [25]. In all five studies [25,31–34], BoP values showed considerable improvement compared to that of their baseline. Mercado et al. [31] could significantly decrease the BoP value by 80% using regenerative surgical therapy, DBBMC, EMD, and doxycycline, indicating the efficacy of this regenerative treatment approach of peri-implantitis. The results of this study also demonstrated that SPT caused a decrease in the BoP after surgical treatment, in which the use of SPT at the four-month interval, compared to that at six-month interval, caused a 60% decrease in BoP in the treated implants, indicating that if SPT extended longer than four months, the risk of inflammation recurrence increased in dental implants, resulting in a deterioration in the maintenance of implants for a long time. Nonetheless, this study [31] used only a single treatment protocol and had no comparison/control groups; thus, determining the effects of the various "cocktail" components on the results of treatment was impossible. Also, the regenerative bone gain was stable in all five studies [25,31–34] after the treatment, meaning that therapeutic approaches could largely inhibit bone loss in the patients. The level of bone was found to be stable in 92.5% of the implants after the surgical treatments [33]. This study [33] also demonstrated that BoP decreased by 75% in the two-year follow-up period, and there was no implant loss. The plaque score in the majority of patients (95%) was less than 10% after surgical treatment at every control visit and decreased by 67.5% at the final period of review compared to that of baseline. The results of this study [33] suggested

that the apically positioned flap and osteoplasty in combination with implantoplasty was an effective and reliable strategy for peri-implantitis treatment but increased gingival recession in aesthetic areas [33]. The results of this study [33] demonstrated that surgical therapy to eliminate pockets combined with an apically positioned flap, osteoplasty, and implant surface smoothing, is a promising approach to inhibiting the progression of peri-implantitis for a period of two years. In addition, it was found that compliance with precise daily control of plaque is of great importance, and the aesthetic outcome can restrict the applicability of this therapeutic method in the anterior maxilla [33]. Certain modifications of treatments following the surgical method were reported by Dalago et al. [32]. In this study [32], the full thickness of the flap increased, and the granulation tissue was eliminated. The treatment protocol was performed in three groups as follows: Group 1: chemical decontamination using 50% citric acid for 3 min; group 2: chemical decontamination using citric acid and harvesting the SCTG from the palate; and group 3: implantoplasty and chemical decontamination. All therapies were effective for the treatment of peri-implantitis, but SCTG maintained the greatest keratinized mucosa width. Therefore, surgical therapies along with mechanical and chemical decontamination were highly effective [32]. Overall, all therapeutic approaches were found to be effective in treating peri-implantitis; however, chemical contamination followed by SCTG was found to be the best therapeutic approach to preserving the keratinized mucosa width.

Mercado et al. [31] used DBBMC and EMD combined with doxycycline as an effective regenerative treatment for peri-implantitis. Furthermore, Mercado et al. [31] demonstrated that surgical therapy using a bone graft at implants with intraosseous lesions could be a viable option. This makes us think about whether bone grafting is a promising approach for the treatment of peri-implantitis. In the literature, while the results of some studies [35,36] demonstrated that the addition of a membrane has a direct benefit in reducing BoP and PPD when a barrier membrane is utilized for covering the bone graft alone [37], Roos-Jansåker et al. [25] did not observe this benefit after the addition of a membrane, demonstrating that further studies are needed to determine the effects of a membrane after covering the bone graft. Moreover, it has been recently demonstrated that the application of some compounds, such as probiotics [38], natural compounds [39], and ozonized water [40], have a significant influence on peri-implant periodontal parameters. Nonetheless, future studies are needed to confirm the effects of these compounds. In this study, the risk of bias was assessed using RoB 2 and ROBINS-I tools for the five included studies, and the results demonstrated that all studies had a low risk of bias. Approximately all of the items met low risk as observed in the follow-up periods of clinical assessments. The randomization, allocation, and blinding were appropriately described.

5. Conclusions

According to the two–five-year follow-up of this systemic review, surgical treatment, including bone substitute material, caused clinical parameters, such as BoP and PPD, to be improved compared to their baseline conditions (before surgical treatment). However, while the reduction of PPD in the Mercado et al. [31], Dalago et al. [32], Englezos et al. [33], and Isler et al. [34] studies was statistically significant, the reduction of this parameter did not show any statistical significance in the Roos-Jansåker et al. [25] study. Therefore, the selection of surgical treatment methods was dependent on the clinical presentation and the level of peri-implantitis defects. In conclusion, among the therapeutic approaches used in these five studies for peri-implantitis treatment, using a combination therapy of deproteinized bovine bone mineral with 10% collagen, enamel matrix derivative, and doxycycline seems to be more appropriate to consider in the clinic to treat peri-implantitis.

6. Limitation of This Study

This systematic review has limitations that might influence the overall validity. First, all five studies selected had a relatively small sample size. Second, the clinical presentation of peri-implantitis among the patients was not equal in the studies; thus, the comparison

of treatment methods might be difficult. Third, the selected studies were only in English; therefore, similar studies reported in other languages might have been missed. Finally, the number of selected studies in this systemic review was only five, and this might not be sufficient to draw a solid conclusion.

Author Contributions: L.A.S. and A.S.: conceptualization. S.W., S.E.A., L.A.S. and A.S.: investigation. S.W.: writing—original draft. S.E.A., L.A.S. and A.S. commented on the manuscript. S.E.A. revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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