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EVALUATION OF COMBINED THERAPIES IN THE SURGICAL TREATMENT OF PERI-IMPLANTITIS: AN INTEGRATIVE REVIEW

ABSTRACT

Periimplantitis is an inflammatory process that affects the tissues around osseointegrated functional implants, promoting progressive loss of supporting bone. This integrative literature review aimed to evaluate the results of different therapies combined with surgical techniques for treating peri-implantitis. A literature search was performed in PubMed and LILACS databases with periimplantitis and surgical treatment descriptors. The selection criteria included randomized controlled clinical trials published in the last five years, in English, with full text, in which surgical techniques treated peri-implantitis. Twelve studies met the inclusion criteria and were submitted for analysis. Four hundred sixty-five patients were evaluated, with a mean follow-up period of 12 months. The therapies combined with surgical techniques were the use of enamel matrix-derived protein (EMD), antibiotic therapy, antimicrobial photodynamic therapy, implantoplasty, glycine blasting, and bone grafts, mainly of alloplastic or xenogeneic origin, which were associated or not with bioresorbable membranes and choline-stabilized orthosilicic acid. Based on the results, the combined therapies with bone grafts were more employed regardless of origin. However, the grafting material of xenogenous origin showed better results in the percentage of filling of the bone defect. Moreover, PDME also showed positive results when used. According to the established problem question, combined therapies associated with surgical techniques are more effective than isolated surgical therapies, and using grafting materials or the PDME presented the best results.

Keywords: peri-implantitis; periodontics; osseointegrated dental implantation.

AVALIAÇÃO DE TERAPIAS COMBINADAS NO TRATAMENTO CIRÚRGICO DA PERI-IMPLANTITE: UMA REVISÃO INTEGRATIVA

RESUMO

A peri-implantite é um processo inflamatório que afeta os tecidos ao redor de implantes funcionais osseointegrados, promovendo a perda progressiva do osso de suporte. Essa revisão integrativa da literatura teve como objetivo avaliar os resultados de diferentes terapias combinadas com técnicas cirúrgicas para o tratamento da peri-implantite. Foi realizada uma pesquisa da literatura nos bancos de dados PubMed e LILACS com os descritores peri-implantite e tratamento cirúrgico. Os critérios de seleção incluíram ensaios clínicos controlados e randomizados publicados nos últimos cinco anos, em inglês, com texto completo, nos quais as técnicas cirúrgicas tratavam a peri-implantite. Doze estudos atenderam aos critérios de inclusão e foram submetidos à análise. Quatrocentos e sessenta e cinco pacientes foram avaliados, em um período aproximado de acompanhamento de 12 meses. As terapias combinadas com as técnicas cirúrgicas foram o uso de proteína derivada da matriz do esmalte (EMD), tratamento com antibióticos, terapia fotodinâmica antimicrobiana, implantoplastia, jateamento de glicina e enxertos ósseos, principalmente de origem aloplástica ou xenogênica, que foram associados ou não a membranas biorreabsorvíveis e ácido ortosilícico estabilizado em colina. Com base nos resultados, as terapias combinadas com enxertos ósseos foram mais empregadas, independentemente da origem. No entanto, o material de enxerto de origem xenógena apresentou melhores resultados na porcentagem de preenchimento do defeito ósseo. Além disso, o PDME também apresentou resultados positivos quando utilizado. De acordo com a questão-problema estabelecida, as terapias combinadas associadas às técnicas cirúrgicas são mais eficazes do que as terapias cirúrgicas isoladas, e o uso de materiais de enxerto ou o PDME apresentaram os melhores resultados.

Palavras-chave: peri-implantite; periodontia; implante dentário osseointegrado.

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1 INTRODUCTION

The 2018 Classification of Periodontal and Peri-implant Diseases and Conditions characterizes peri-implantitis (PI) as an inflammatory process that affects the peri-implant mucosa and promotes the continuous loss of supporting bone tissue (Schwarz *et al*., 2018; Berglundh *et al*., 2018). According to Salvi *et al*., PI is the leading cause of dental implant loss (Salvi; Cosgarea; Sculean, 2017). Risk factors can predispose the individual to have the development of a clinical picture of PI, being able to cite the previous or current history of periodontitis, Diabetes Mellitus, inadequate control of the bacterial plate, and smoking as the main factors (Daubert *et al*., 2015; Ferreira *et al*., 2006; Costa *et al*., 2011; Ross-Jansaker *et al*., 2006). Evidence suggests that iatrogenic conditions, eight genetic factors, nine absence of keratinized mucosa, ten may, in a certain way, favor or promote the necessary conditions for the perpetuation of PI (Lang; Berglund, 2011; Laine *et al*., 2006; Gobbato *et al*., 2013). About the diagnosis of PI, clinical features of inflammation, presence of suppuration and bleeding, increased probing depth, radiographic bone loss compared to initial examinations can be observed. However, there are cases of impossibility of comparison with previous exams due to the lack of registration of the aforementioned parameters (Berglundh *et al*., 2018; Schwarz *et al*., 2018). Thus, bone loss greater than 3mm associated with bleeding and probing depth equal to or greater than 6mm should be considered for the correct diagnosis of PI (Berglundh *et al*., 2018; Schwarz *et al*., 2018).

Non-surgical therapy is commonly used in the treatment of PI, which consists of mechanical debridement of the infected site with curettes or ultrasonic devices, and may also be associated with blasting techniques, antimicrobial drugs, laser therapy, and photodynamic therapy (Tastepe *et al*., 2013; Javed *et al*., 2013; Yamamoto; Tanabe, 2013; Deppe *et al*., 2013). However, according to the complexity of the peri-implant infection, methods combined with surgical techniques should be used to favor the maintenance of the implant and to heal and prevent the remission of the infectious condition. Several techniques are reported in the literature, among them implantoplasty, regenerative therapies with bone grafts and/or membranes, methods of superficial decontamination, and other therapeutic approaches (Romeo *et al*., 2007; Wiltfang *et al*., 2012; Schwarz *et al*., 2006; Waal *et al*., 2013). Thus, this integrative review aims to verify in the literature which combined therapies associated with surgical techniques can be used in the treatment of PI and which have the best results in their treatment.

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2 MATERIALS AND METHODS

2.1 Search strategy

The purpose of this literature review was to determine the theme and formulate the following problem question, according to the PICO strategy: “In patients diagnosed with peri-implantitis, are combined therapies more effective than isolated surgical therapies?” (Miller; Forest, 2001 Souza *et al*., 2007). The search was carried out in the scientific databases of PubMed/Medline (National Library of Medicine) and LILACS (Library of Latin American and Caribbean Literature in Health Sciences), thus fulfilling the requirement of at least two databases for the execution of reviews by the AMSTAR-2 Instrument of reviews. The descriptors used in this review were registered on the MeSH platform (Medical Subject Headings) and DeCS (Health Science Descriptors), linked, respectively, to the National Library of Medicine (NLM) and the Latin American and Caribbean Center on Health Sciences Information (BIREME). The article search process was performed by combining the terms in pairs with the Boolean operator “AND” and “OR”, namely: “peri-implantitis” and “surgical treatment”. It is essential to mention that natural language descriptors, such as “surgical treatment,” included studies that did not present controlled and indexed language and collected articles until December 2021.

2.2 Selection of studies

Initially, the articles were analyzed by two independent evaluators (OAPV; JCN) by reading the title, abstract, and descriptors to verify if they presented agreement with the area of interest. If there were doubts from the evaluators regarding whether the study would fit in the first stage of analysis, a third evaluator (VCNN) was consulted, making the final decision. It is essential to mention that duplicate publications were removed using the Mendeley Desktop (Mendeley Desktop, v1.19.4; Elsevier) software, also used to manage references. Subsequently, the selected articles were submitted for a complete critical analysis, capturing and tabulating the data.

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2.3 Inclusion and exclusion criteria

As inclusion criteria, controlled and randomized clinical studies were selected, published in the last five years in English, with full text available in full, in which the surgical treatment of peri-implantitis should be approached as a test therapeutic proposal, with no obligation to this conduct in the treatment of the control group. Studies that did not meet the criteria were excluded.

2.4 Evaluation of Studies

Two independent evaluators analyzed the studies, and the data were tabulated in tables predefined by the researchers. If there were doubts about any of the evaluation items, a third evaluator was consulted, making the final decision. The items evaluated in this review are the surgical procedures and complementary therapy used in the test groups, peri-implant parameters, radiographic data, follow-up period, sampling applied in the studies, the presence of environmental and systemic conditions, pre-and postoperative preparation protocol of the intervention bed, and postoperative complications. However, if the author(s) did not report any of the data, the other clinical information from the study was considered since a quantitative data analysis was not performed for this integrative review.

3 RESULTS

A total of 1,279 studies were found in the databases, and after the initial selection and application of the criteria, 13 articles were included in this review. In more detail, 1.210 articles were found in PubMed and 68 in LILACS; results can be seen in the flowchart, which was modified according to the PRISMA 2020 protocol (Table 1). Figure 1 flowchart of the selection process (Page *et al*., 2021).

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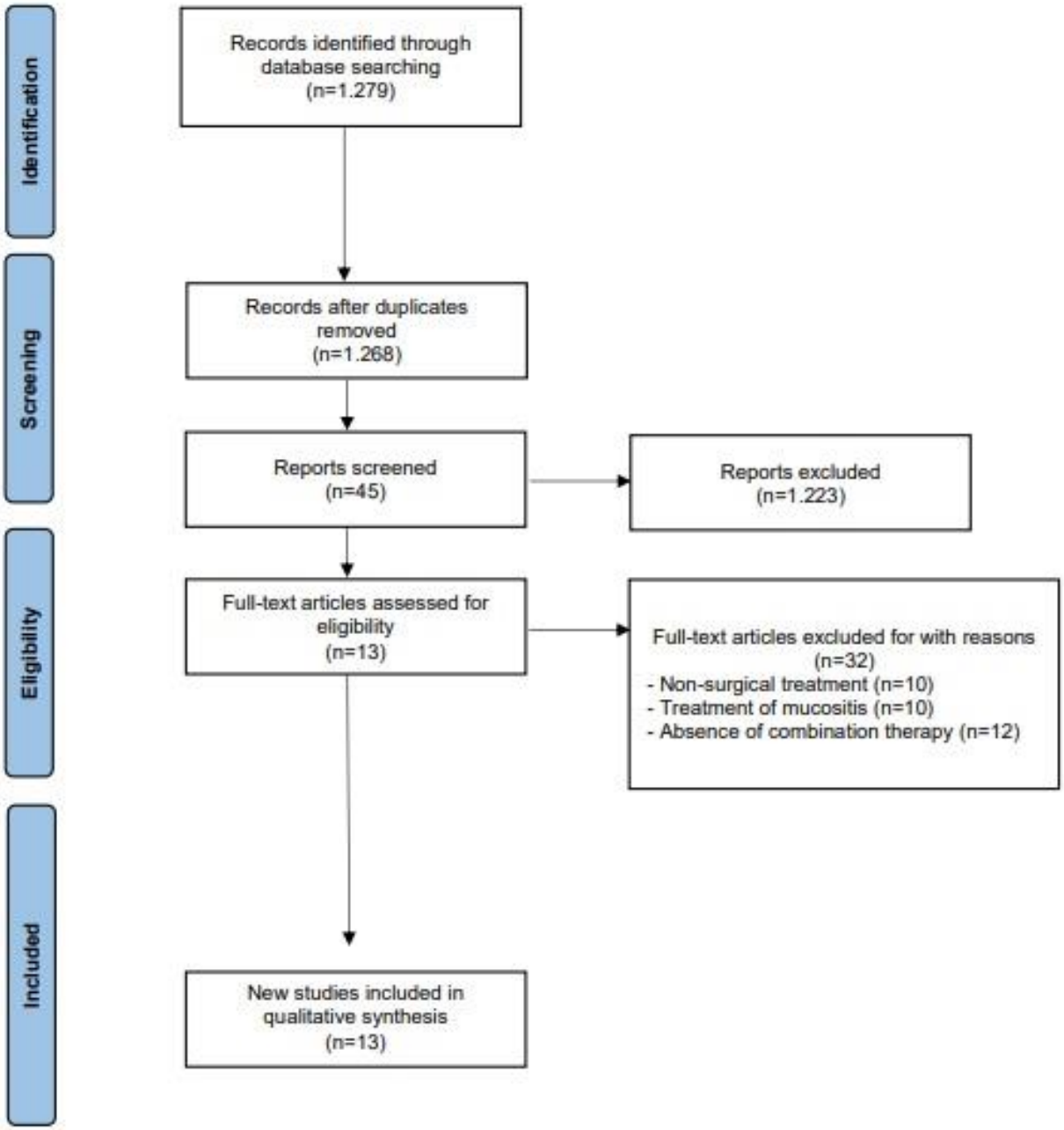
Figure 1. flowchart of the selection process.



Source: from the authors themselves.

Table 1 - Articles included.

AUTHOR	PERIODICAL	TITLE	CONCLUSION
Carcuac *et al., (2017)*	Journal of Clinical periodontology	Surgical treatment of peri-implantitis: 3-year results from a randomized controlled clinical trial	It is suggested that surgical treatment of peri-implantitis is effective and that the therapy's results are affected by the characteristics of the implant surface. The potential benefits of systemic antibiotics are not sustained for more than three years.
Lasserre, Brecx,	The International Journal of Oral & Maxillofacial Implants	Implantoplasty Versus Glycine Air Abrasion for the Surgical Treatment	Within the limitations of this 6-month follow-up study, implantoplasty is as effective as glycine air polish for the surgical treatment of peri-implantitis.

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Tomas (2020)		of Peri-implantitis: A Randomized Clinical Trial	
Isler *et al., (2018)*	Clinical Implant Dentistry and Related Research	Regenerative surgical treatment of peri-implantitis using either a collagen membrane or concentrated growth factor: A 12-month randomized clinical trial	The results of the present study suggest that both regenerative approaches significantly improved clinical and radiographic assessments. The collagen membrane procedure in combination with bone substitute showed better results at 12 months in peri-implantitis RST.
Isehed *et al., (2018)*	Journal of Clinical Periodontology	Surgical treatment of peri-implantitis using enamel matrix derivative, an RCT: 3- and 5-year follow-up	An exploratory analysis suggests that adjuvant DME is positively associated with implant survival for up to 5 years, but more extensive studies are needed.
Polymeri *et al., (2020)*	Clinical Oral Implants Research	Surgical treatment of peri-implantitis defects with two different xenograft granules: A randomized clinical pilot study	Within this pilot study's limitations, the EB xenograft application proved to be non-inferior to the BO xenograft when used in reconstructive surgery of peri-implant bone defects.
Cha, Lee, Kim (2019)	Journal of Dental Research	Surgical Therapy of Peri-Implantitis with Local Minocycline: A 6-Month Randomized Controlled Clinical Trial	These findings indicate that repeated local administration of minocycline combined with surgical treatment offers significant benefits in terms of clinical parameters and radiographic bone filling, with a higher treatment success rate in the short healing period.
Renvert, Roos-Jansåkee, Persson (2018)	Journal of Clinical Periodontology	Surgical treatment of peri-implantitis lesions with or without the use of a bone substitute-a randomized clinical trial	The successful outcome of treatment using a bone substitute was more predictable when a composite therapeutic outcome was considered.
Isehed *et al., (2016)*	Journal of Clinical Periodontology	Effectiveness of enamel matrix derivative on the clinical and microbiological outcomes following surgical regenerative treatment of peri-implantitis. The randomized controlled trial	Adjuvant DME to surgical treatment of peri-implantitis was associated with the prevalence of Gram+/aerobic bacteria during the follow-up period and increased marginal LB 12 months after treatment.
Hallström *et al., (2017)*	Journal of Clinical Periodontology	Open flap debridement of peri-implantitis with or without adjunctive systemic antibiotics: A randomized clinical trial	Surgical treatment of peri-implantitis with adjuvant systemic azithromycin did not provide 1-year clinical benefit compared to those who received only open flap debridement.
Tapia B *et al., (2019)*	Journal of Clinical Periodontology	The adjunctive effect of a titanium brush in implant surface decontamination at peri-implantitis surgical regenerative	Additional use of a titanium brush during regenerative treatment of peri-implantitis resulted in statistically significant benefits in terms of PS reduction after 12 months.

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		interventions: A randomized controlled clinical trial	
Albaker *et al., (2018)*	Photodiagnosis and Photodynamic Therapy	Effect of antimicrobial photodynamic therapy in open flap debridement in the treatment of peri-implantitis: A randomized controlled trial	The single application of a PDT as an adjunct to OFD does not provide additional benefits in improving peri-implant clinical and radiographic parameters in peri-implantitis.
Wang *et al.*, (2021)	Journal of Clinical Periodontology	Laser-assisted regenerative surgical therapy for peri-implantitis: A randomized controlled clinical trial	Peri-implantitis regenerative therapy may help reduce PD probing. However, a larger sample size and longer follow-up are needed to confirm whether Er: YAG laser irradiation provides additional clinical benefits for regenerative therapy of peri-implantitis.
Teughels *et al.*, (2021)	BMC Oral Health	The effect of choline-stabilized orthosilicic acid in patients with peri-implantitis: an exploratory randomized, double-blind, placebo-controlled study	Orthosilicic acid can stabilize and even prevent further bone loss after surgical treatment of peri-implantitis and support mucosal tissue healing.

Source: from the authors themselves

Regarding the precepts of compliance with ethical standards of experimentation, only Albaker *et al*., (2018) and Wang *et al*., (2021), did not inform the approval protocol number in the regulatory of the linked institutions; they only mentioned that they met the requirements of the Helsinki declaration or that the institution approved all protocols of the study.

In the total of selected studies, 465 patients were evaluated, with an average follow-up period of 12 months, in which several therapies combined with surgical techniques were analyzed, such as enamel matrix-derived protein, antibiotic therapy, antimicrobial photodynamic therapy, implantoplasty associated with glycine blasting, bone grafts and choline-stabilized orthosilicic acid (Albaker *et al*., 2018; Wang *et al*., 2021; Isehed *et al*.,2018; Isehed *et al*., 2016; Hallstrom *et al*., 2017; Cha; Lee; Kim, 2019; Carcuac *et al*., 2017; Lasserre; Brecx; Tomas *et al*., 2020; Renvert; Ross-Jansaker; Persson, 2018; Tapia *et al*., 2019; Isler *et al*., 2018; Polymeri *et al*., 2020; Teughels *et al*., 2021). Regarding clinical parameters, the most evaluated peri-implant indices in the studies were bleeding on probing (SS), probing depth (PS), suppuration on probing, and bacterial plaque index (BPI) (Table 2 and 3) (Albaker *et al*.,2018; Wang *et al*., 2021; Isehed *et al*., 2018; Isehed *et al*., 2016; Hallstrom *et al*., 2017; Cha *et al*., 2019; Carcuac *et al*., 2017; Lasserre; Brecx; Tomas *et al*., 2020; Renvert; Ross-Jansaker;

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Persson, 2018; Tapia *et al*., 2019; Isler *et al*., 2018; PolymerI *et al*., 2020; Teughels *et al*., 2021) (Table 2 and 3).

Table 2 - Data from the therapeutic protocols.

AUTHOR	OBJECTIVE	TEST	CONTROL	RESULT
Renvert, Roos-Jansåker, Persson (2018)	Comparative analysis of combined therapy of surgical debridement and chemical disinfection of the SI or combination of combined therapy with Endobon®Xenograft bone graft (Zimmer Biomet).	Mechanical debridement with titanium curettes, decontamination of the SI with 3 % H_2O_2, double irrigation with 20mL of SS and filling of the intraosseous defect with Endobon®Xenograft (Zimmer Biomet) associated with the patient's blood.	Mechanical debridement with titanium curettes, decontamination of the SI with 3% H_2O_2 double irrigation with 20mL saline and closure of the surgical site with a flap.	A significant difference was observed in the test group (EndoBon®Xenograft), regarding the filling of the defect.
Isehed *et al.* (2018)	Evaluate clinical and radiographic outcomes after surgical treatment with or DME.	Mechanical cleaning with an ultrasonic cleaner with a special implant tip, titanium instruments, combined with Sodium Chloride 9mg/ml 2x20ml rinse and placement of EMD at the implant site prior to flap closure.	Mechanical cleaning with ultrasonic cleaner with a special implant tip, titanium instruments, combined with 9mg/ml 2x20ml sodium chloride rinse and flap closure.	EMD presents a better result in the survival rate of implants at 3 and 5 years
Isehed *et al.* (2016)	To compare the radiological, clinical and microbial effects of surgical treatment alone or in combination with DME	Mechanical cleaning with ultrasonic cleaner with a special implant tip, titanium instruments, cotton gauze cleaning and superfloss followed by rinsing with sodium chloride solution (9mg/ml 2x20ml), application of 0.3 of Emdogain® in the lower part of the bone defect and flap closure.	Mechanical cleaning with ultrasonic cleaner with implant tip, titanium instruments, cleaning with cotton gauze and superfloss followed by rinsing with sodium chloride solution (9mg/ml 2x20ml and flap closure.	Significant result in the DME group.
Albaker *et al.* (2018)	To evaluate the effects of aPDT as an adjunct to open flap debridement.	Clean implant with sterile curettes and cotton gauzes with sun. Saline, application of 0.005% methylene blue to the periodontal pocket and left in place for 10 seconds, 670 nanometer Diode Laser irradiation at 150 optical fiber diameter of 0.06 mm for 1 minute in each periodontal pocket using a flexible tip.	Clean implant with sterile curettes and cotton gauze with SS and flap closure	There was no significant difference between the groups in the follow-up period.
Tapia *et al.* (2019)	To evaluate the use of the titanium brush as an additional mechanical approach	Mechanical decontamination with plastic curettes and ultrasonic devices, titanium brush at low oscillating speed	Mechanical decontamination with plastic curettes and ultrasonic devices,	Better results of the test group, especially in bone filling.

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	during regenerative surgery.	(900rpm), intraosseous defect filled with alloplastic material (β- Tricalcium Phosphate hydroxyapatite) and covered by a collagen membrane.	intraosseous defect filled with alloplastic material (β- Tricalcium Phosphate hydroxyapatite) and covered by a collagen membrane.	
Hallström *et al.* *(2017)*	To compare the clinical, radiographic and microbiological outcome after open flap debridement with and without antibiotics.	Mechanical cleaning of the implant, debridement of the open flap with sterile curettes and cotton gauze soaked in SS, flap closure, Zithromax ® 250mg 2x on the day of surgery and 1x/day for 4 days.	Mechanical cleaning of the implant, debridement of the open flap with sterile curettes and cotton gauze soaked in SS, flap closure.	No significant differences between groups.
Wang *et al.* (2021)	Evaluate the benefits of Er:YAG laser as an adjuvant to regenerative surgical therapy	Mechanical debridement with open flap, supracrestal, implantoplasty, bone graft with a mixture of human allograft with demineralized bone, human matrix allograft mass and covered with acellular dermal matrix membrane. Using the Er:YAG laser .	Mechanical debridement with open flap, supracrestal, implantoplasty, bone graft with a mixture of human allograft with demineralized bone, human matrix allograft mass and covered with acellular dermal matrix membrane.	No significant intergroup differences
Isler *et al*. (2018)	Comparative analysis of combined therapy with two bioresorbable barrier membranes, collagen membrane (CM) or concentrated growth factor (CGF).	Mechanical debridement with titanium curettes, decontamination of the SI with SS and filling with a bone substitute (Gânu os Bio), two pieces were used as a barrier over the bone substitute.	Mechanical debridement with titanium curettes, SI decontamination with SS, filled with intraosseous substitute and covered with CM, closure with flaps.	Bone graft with collagen membrane showed better results.
Lasserre, Brecx, Tomas, (2020)	Comparative analysis of implantoplasty and air glycine polishing.	Flap made with Lucas Curette and hard deposits with Plasteel Columbia universal curettes, decontamination with SS 20ml. Resective approach, and use of drills for access. Irrigation for decontamination with SS.	Flap made with Lucas curette and hard deposits with Plasteel Columbia universal curettes, decontamination with SS 20ml. Air- Flow treated implant surface Perio and glycine amino acid powder and finally irrigated with SS.	No significant differences in the intergroup analysis.
Cha, Lee e Kim (2019)	To determine the clinical, radiographic and microbial effect of local minocycline with the surgical	SI cleaned with titanium coated curettes (Gracey Hu-Friedy), copper metal alloy ultrasonic scraper tip, titanium brush (Dentium) and air powder abrasive device (Air-	SI cleaned with titanium coated curettes (Gracey Hu-Friedy), copper metal alloy ultrasonic scraper tip, titanium brush	The test group showed significant results regarding defect filling and improvement in clinical parameters.

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	treatment of peri-implantitis.	FlowMaster). 1mg of minocycline ointment was applied to SI.	(Dentium) and air powder abrasive device (Air- FlowMaster). 1mg of placebo ointment was applied to SI.	
Polymeri *et al.* (2020)	Assessing the reconstructive potential of BE (Endobon) is not inferior to that of BO (Bio-Oss) when applied to intraosseous defects peri implant.	Removed granulation tissue with titanium curettes (HuFriedy), implant threads decontaminated with 3% H_2O_2 for 1min, rinse with SS. Filled with Endobon.	Removed granulation tissue with titanium curettes (HuFriedy), implant threads decontaminated with 3% H_2O_2 for 1min, rinse with SS. Filled with Bio-Oss.	No differences were observed in the intergroup analysis. Similar results.
Carcuac *et al.* (2017)	To report the 3-year follow-up of patients on surgical treatment of peri advanced implantitis.	**G1:** Amoxicillin 2x750mg daily/mechanical decontamination of the SI by 0.2% chlorhexidine digluconate solution. **G2**: Systemic antibiotic/ mechanical decontamination of SI with SS. **G3:** no systemic antibiotics/IS decontamination by antiseptic agent.	**G4:** No systemic antibiotics and no SI decontamination with SS.	Implant surface characteristics had a significant impact on 3-year outcomes in favor of implants with unmodified surfaces.
Teughels *et al.* (2021)	Investigate the effect of oral administration of choline-stabilized orthosilicic acid on clinical symptoms of peri-implantitis and associated bone loss	Flap followed by mechanical debridement with titanium curettes, SI decontamination with EDTA gel. Oral administration of placebo with 520 mg microcrystalline cellulose beads	Flap followed by mechanical debridement with titanium curettes, SI decontamination with EDTA gel. Oral administration of AOC (520 mg of beads containing 5 mg of silicon and 100 mg of choline)	Stability in radiographic records, remaining stable in the test group.

Abbreviation: PD = Probing depth; BoP= Bleeding on probing; PMMR= peri-implant mucosa margin recession; BPI= Bacterial Plaque Index; BL= bone level; MPS= mouth plaque score; TMBS= total mouth bleeding score; SoP= suppuration on probing; MGR= marginal gingival recession; MBL=marginal bone level; GI= gingival index; RIL= relative insertion level; SS= saline solution; SI= implant surface; EMD= protein derived from the enamel matrix; CAL = Clinical Attachment Loss; EDTA= Ethylenediamine tetraacetic acid.
Source: from the authors themselves.

Table 3 - Sampling evaluation data.

AUTHOR	SAMPLING	PERI-IMPLANT INDEXES	RADIOGRAPHIC PARAMETERS	FOLLOW-UP PERIOD
Renvert, Roos-Jansåker, Persson (2018)	41 patients	PD, BoP, BPI and PMMR	Distance from the implant platform to the most coronal bone/filling of the defect until the implant contact mesial and distal.	12 months

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Isehed *et al.* (2018)	25 patients	BoP, SoP and BP	Bone level on the mesial and distal surfaces measured from a reference point on the implant to the bottom of the bone defect.	60 months
Isehed *et al.* (2016)	25 patients	MPS, TMBS, BoP, BPI, SoP, and PMMR	NO change over the test period.	12 months
Albaker *et al.* (2018)	24 patients	BPI, BoP, PD, and MBL	Distance from the implant platform to the alveolar bone crest.	12 months
Tapia *et al.* (2019)	30 patients	BPI, BoP, SoP, PD, PMMR	Bone level measuring the distance between the implant shoulder and the bottom of the defect, intraosseous defect measuring the distance between the bottom of the defect and the line connecting the distal and mesial interproximal bone crest.	12 months
Hallström *et al. (2017)*	39 patients	PD, BoP, BPI, SoP	Distance between implant thread pitch lengths.	12 months
Wang *et al.* (2021)	24 patients	PD, CAL, GI, PMMR, BPI, SS	Linear bone gain and bone defect filling measured through a constant radiographic reference for each patient (platform or abutment porcelain junction).	6 months
Isler *et al.* (2018)	52 patients	BoP, BPI, GI, PMMR, PD	Distance from the implant platform to the most coronal bone/filling of the defect until the implant contact mesial and distal.	12 months
Lasserre, Brecx, Toma (2020)	31 patients	BPI, BoP, SoP, PS, RMMP, RIL	Distance from the implant platform to the most coronal bone/filling of the defect until the implant contact mesial and distal.	6 months
Cha *et al.* (2019)	46 patients	GI, BPI, PD, BoP, SoP	Distance from the implant platform to the most coronal bone/filling of the defect until the implant contact mesial and distal.	6 months
Polymeri *et al.* (2020)	24 patients	PD, BoP and SoP	Distance from the implant platform to the most coronal bone/filling of the defect until the implant contact mesial and distal.	12 months
Carcuac *et al.* (2017)	83 patients	PD, BoP, SoP and NOM	Pitch distance between implant threads for calibration.	3 years
Teughels *et al.* (2021)	21 patients	PD, BoP and PMMR	Distance from implant shoulder to alveolar crest and distance from implant shoulder to first bone-implant contact.	12 months

PD= Probing depth; BoP= Bleeding on probing; PMMR= peri- implant mucosa margin recession; BPI= Bacterial Plaque Index; BL= bone level; MPS= mouth plaque score; TMBS= total mouth bleeding score; SoP= suppuration on probing; MGR= marginal gingival recession; MBL=marginal bone level; GI= gingival index; RIL= relative insertion level; IS-AC: distance from the implant shoulder to the alveolar crest; IS-BIC: distance from implant shoulder to first bone-implant contact.
Source: from the authors themselves.

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Regarding the selection criteria for the sampling of studies, patients with systemic conditions, such as Diabetes Mellitus, were excluded from the sample; smokers, patients with previous use of antibiotics, anti-inflammatory drugs, drugs that harmed gingival growth, with active periodontitis and not undergoing treatment, consumption of alcoholic beverages, individuals under 18 years of age or who were participating in another clinical study (Albaker *et al*., 2018; Wang *et al*., 2021; Isehed *et al*., 2018; Isehed *et al*., 2016; Hallstrom *et al*., 2017; Cha; Lee; Kim, 2019; Carcuac *et al*., 2017; Lasserre; Brecx; Tomas *et al*., 2020; Renvert; Ross-Jansaker; Persson, 2018; Tapia *et al*., 2019; Isler *et al*., 2018; Polymeri *et al*., 2020; Teughels *et al*., 2021). In addition, the studies considered, for inclusion of the target population, individuals who had one or more sites per implant with a probing depth (PD) of 4 mm, combined with SS/suppuration and marginal bone loss in the peri-implant region (Albaker *et al*., 2018; Wang *et al*., 2021; Isehed *et al*., 2018; Isehed *et al*., 2016; Hallstrom *et al*., 2017; Cha; Lee; Kim, 2019; Carcuac *et al*., 2017; Lasserre; Brecx; Tomas *et al*., 2020; Renvert; Ross-Jansaker; Persson, 2018; Tapia *et al*., 2019; Isler *et al*., 2018; Polymeri *et al*., 2020; Teughels *et al*., 2021) (Table 3).

Among the radiographic parameters evaluated, the distance from the implant platform to the bone crest and filling of the bone defect until the implant contact in the mesial and distal was used (Albaker *et al.*, 2018; Wang *et al*., 2021; Isehed *et al.*, 2018; Isehed *et al*., 2016; Hallstrom *et al.*, 2017; Cha; Lee; Kim, 2019; Carcuac *et al*., 2017; Lasserre; Brecx; Tomas *et al.*, 2020; Renvert; Ross-Jansaker; Persson, 2018; Tapia *et al*., 2019; Isler *et al*., 2018; Polymeri *et al.*, 2020; Teughels *et al.*, 2021). Regarding the preoperative protocols, 3 authors did not specify the protocols (Hallstrom *et al.*, 2017; Carcuac *et al*., 2017; Renvert; Ross-Jansaker; Persson, 2018) and most authors performed oral hygiene instruction, mechanical/ultrasonic subgingival debridement and irrigation with 0.12% Chlorhexidine Digluconate as prepared at the affected site; used (Albaker *et al.*, 2018; Wang *et al*., 2021; Isehed *et al.*, 2018; Isehed *et al*., 2016; Cha; Lee; Kim, 2019; Lasserre; Brecx; Tomas *et al.*, 2020; Tapia *et al*., 2019; Isler *et al*., 2018; Polymeri *et al.*, 2020; Teughels *et al.*, 2021), only 1 did not report the postoperative management (Carcuac *et al*., 2017), the other studies mainly instructed patients to perform a mouthwash with 0.2 or 0.12% Chlorhexidine Digluconate for 2 to 6 weeks, in addition to being submitted to prophylaxis every 3 months and drug therapy (Albaker *et al.*, 2018; Wang *et al*., 2021; Isehed *et al.*, 2018; Isehed *et al*., 2016; Hallstrom *et al.*, 2017; Cha; Lee; Kim, 2019; Lasserre; Brecx; Tomas *et al.*, 2020; Renvert; Ross-Jansaker; Persson, 2018; Tapia *et al*., 2019; Isler *et al*., 2018; Polymeri *et al.*, 2020; Teughels *et al.*, 2021) (Table 4).

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Table 4 - Pre and postoperative patient care data.

AUTHOR	PREOPERATIVE PROTOCOL	POSTOPERATIVE PROTOCOL
Renvert, Roos-Jansåker, Persson (2018)	Not specified.	Antibiotic therapy with Zitromax 500mg 1x/day after surgery and 250mg 1x for 4 days, Ibuprofen 400mg 3x/day for 2 days. Mouthwash with chlorhexidine 2x/day. Dental prophylaxis every 3 months.
Isehed *et al.* (2018)	Oral hygiene instruction and non-surgical treatment.	Rinse 2x daily with 10ml of 2mg/ml chlorhexidine for 6 weeks, do not chew or brush on the treated side for 2 weeks. Use of soft toothbrush and proximal brushes.
Isehed *et al.* (2016)	oral hygiene instruction and non-surgical treatment.	Rinse 2x daily with 10ml of 2mg/ml chlorhexidine for 6 weeks, do not chew or brush on the treated side for 2 weeks. Use of soft toothbrush and proximal brushes.
Albaker *et al.* (2018)	Non-surgical treatment, combining manual instruments and ultrasound.	Augmentin 625mg and ibuprofen 400mg 3x/day after surgery for 7 days. Mouthwash with 0.2% chlorhexidine for 2 weeks. Soft toothbrush and antiseptic toothpaste.
Tapia *et al*. (2019)	Oral hygiene, subgingival scaling with plastic curettes and irrigation with chlorhexidine digluconate (CHX) 0.12% of affected implants.	CHX mouthwash 0.12% 2x/day for 2 weeks, Amoxicillin 500mg+ Metronidazole 500mg 3x/day for 7 days, in case of allergy, Clindamycin 300mg 6/6h was used. Prophylaxis every 3 months
Hallström *et al. (2017)*	Not specified	Rinse with Chlorhexidine (Hexident 0.2%), super soft brushes, do not brush the treated area until the sutures are removed, prophylaxis every 3 months.
Wang *et al.* (2021)	Subgingival oral prophylaxis with peizo - instruments and stainless-steel hand scrapers	Amoxicillin 500mg 3x/day for 10 days, in case of allergy Azithromycin 250mg 2tablets on the first day and one tablet a day for 4 days, ibuprofen 600mg in case of pain, rinse with chlorhexidine for 1minute 2x/day for 1 week, avoid brushing and touching the operated area for 2 weeks
Isler *et al*. (2018)	Sub/ supragingival debridement. Oral hygiene instruction.	Amoxicillin 500mg + Metronidazole 500mg 3x a day for a week. Mouth rinse with 0.12% chlorhexidine twice a day for 2 weeks. Ibrupofen 100mg 3 a day for the first 3 days.
Lasserre, Brecx, Toma (2020)	Oral hygiene instruction. Periodontal/ peri-implant cleaning supragingival using scrapers, polishing paste and rubber cups.	Rinse with 0.2% chlorhexidine for 1 minute twice a day for 10 days. Ibuprofen 600mg 3x a day for 2 days and Paracetamol 1g if necessary.
Cha, Lee, Kim (2019)	Supragingival cleaning and the same type of toothbrush and toothpaste (Sunstar) for all patients.	Amoxicillin 500mg and Ibuprofen 600mg 3x a day for 3 days.
Polymeri *et al*. (2020)	Amoxicillin 500mg 3x daily and metronidazole 500mg 2x daily starting the day before surgery.	Amoxicillin 500mg 3x a day and metronidazole 500mg 2x a day for 8 days. Paracetamol 500mg if needed. Mouthwash with 0.12% chlorhexidine twice a day for 4 weeks.
Carcuac *et al*. (2017)	Not specified.	Not specified.
Teughels *et al*. (2021)	Oral hygiene instruction, indicating the same items for mechanical plaque control.	Not specified.

Abbreviation: RAR= Scaling and root planning. **Source:** the authors themselves.

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4 DISCUSSION

PI is an inflammatory and progressive condition that promotes changes in soft and hard tissue, compromising the functionality of dental implants (Khammissa *et al*., 2012). When a non-surgical approach does not resolve the infected sites, the surgical approach should be considered (Figuero *et al*., 2014). Thus, surgical treatment combined with complementary therapies is being used to increase the predictability of stability or regression of the clinical picture of IP (Smeets *et al*., 2014; Figuero *et al*., 2014). This integrative literature review aimed to verify whether combined therapies are more effective in patients diagnosed with PI than isolated surgical techniques.

In the present review, three articles evaluated the effects of antibiotic therapy associated with the surgical treatment of PI. Hallström *et al*., (2017), verified the effectiveness of systemically administered azithromycin as an adjunct to mechanical debridement in 39 patients with a 12-month follow-up, and no relevant results were observed in the intergroup analysis or that presented any parameter that justified its use. Carcuac *et al*., (2017), evaluated the effect of amoxicillin administered systemically for three years in 83 patients. The authors observed that administering Amoxicillin 3 times a day, with a concentration of 750mg, had positive results in the peri-implant tissues, in addition to stabilizing the level of peri-implant marginal bone tissue during the follow-up period. Cha, Lee, and Kim (2019) performed the local application of minocycline associated with transsurgical debridement in 46 individuals, with a follow-up period of 6 months; promising results were observed, mainly related to the reduction of GI, PD, and filling of the defect bone. Despite the results, it should be mentioned that the available evidence for the systemic administration of antibiotics (ASA) associated with the surgical treatment of PI is still scarce and in the early stage of development of study protocols (Verdugo *et al*., 2015). Studies like Øen *et al*.,(2021) and Khan *et al*., (2020) demonstrated in their results that ASA use is not justified in combination with surgical therapy.

Implantoplasty is a treatment modality for PI that promotes the modification of the exposed implant surface, promoting a smooth surface, allowing the decontamination of the site, do not cause biological and mechanical complications in the short and medium term to favor osseointegration (Teughels *et al*.,2006; Aljateeli; Fu; Wang *et al*., 2011; Stavropoulos *et al*.,2019). Authors such as Lasserre, Brecx, and Tomas (2020) evaluated the decontamination of the implant surface with or without implantoplasty and air polishing with glycine in 31 patients, with no significant results being observed in the intergroup analysis in the 6-month

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follow-up period. In the study by Esteves *et al*., (2021), they recommended IMP as a form of treatment for peri-implantitis due to the reduction of peri-implant indicators such as BoP, SoP, and to increase the success rate of treated implants, data supported by Beheshti-Maal and Verket (2021). In addition, implant surface decontamination methods can be associated with implantoplasty; in this aspect, glycine presents itself as a biological component that can be used due to its low toxicity, anti-inflammatory activity, and for promoting minimal change in morphology surface of the implants due to their granulation (Matsubara *et al*.,2019; Petersika *et al*., 2008). Although studies in the literature recommend implantoplasty in the surgical treatment of PI, the effect of glycine by abrasion still needs to be evident. Its clinical applicability needs to be improved. Only the study included in this review and the record of a clinical case of Seki *et al*. (2022) have been reported to date.

Bone graft materials are used to treat PI to promote the filling of the bone defect and consequently allow the reosseointegration of the affected implant (Mordini *et al*., 2021). BioOss® is commonly used in treating PI due to the reduction of bone loss in the peri-implant region, promoting the improvement of clinical parameters favoring bone neoformation and osseointegration (Matarasso *et al*., 2021). Endobon® is a deproteinized and lyophilized xenograft of bovine origin; due to its structural characteristics, it allows penetration of osteoblastic cells and intensifies the neoformation of bone tissue. However, it still has little data in the literature. (Hing; Best; Bonfiled, 1999). Among the studies that evaluated methods of bone grafting, Polymeri *et al*. (2020) obtained similar results in the groups with Bio-Oss® and Endobon®, which showed the same efficacy in the clinical improvement of the bone defect. The data are supported by the Aghazadeh, Persson, and Renvert (2012) studies, which obtained more excellent radiographic filling of the bone defect (RFBD) in the Bio-Oss® group and improvement in clinical parameters BoP, SoP, and PD. Similar results were obtained in the study by Renvert, Ross-Jansaker, and Persson (2018) concerning Endobon®, which presented significant data in the RFBD, one of the studies included in this review. Histological and clinical data suggest that Endobon ® has a reconstructive potential similar to Bio-Oss® when used for grafts in fresh sockets after tooth extraction (Barone *et al*., 2013).

The aPDT consists of the use of a photosensitizer associated with a visible or ultraviolet light source at a specific wavelength, promoting damage to the bacterial structure and is capable of accelerating bone repair and favoring osseointegration (Takasaki *et al*., 2009; Shibli *et al*., 2003). Albaker *et al*, (2018), evaluated the effectiveness of aPDT using a methylene blue diode laser as a photosensitizer at a wavelength of 670 nm, with 1-minute exposure at each site in

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patients with peri-implantitis. However, no significant results were observed in the intergroup analysis, mainly in the NOM, PD, BoP, and BPI, in the 12-month follow-up period (Albaker *et al*., 2018). The results obtained by the authors can be justified because the protocol used, the power used of light, photosensitizer, and the irradiation time used influenced the results to be obtained. However, authors such as Lopez *et al*. (2020), and Rastelli (2021), demonstrated that due to the lack of standardization of aPDT studies and protocols, clinical applicability in the treatment of PI is still not recommended (Lopez *et al*., 2020; Souza *et al*., 2021).

There is a variety of high-power lasers that can be used in the treatment of PI; among them, the Er:YAG laser, diode, and carbon dioxide (CO2) can be used since they do not promote changes in the surface morphology of titanium and present favorable results in the improvement of clinical parameters, such as PD reduction, BPI and RIL (Lin *et al*., 2018; Ashnagar *et al*., 2014; Rokaya *et al*., 2020). In the study by Wang *et al*., (2021), 24 patients underwent open-field debridement with an IMP, autogenous and xenogenous bone graft, covered with acellular dermal matrix membrane being associated or not with the use of Er:YAG laser. The authors did not observe significant differences in the inter-group analysis of the parameters evaluated (Wang *et al*., 2021). The results found corroborate the findings of Schwarz *et al*., (2011), Schwarz *et al*., (2012) and Schwarz *et al*., (2013), who used regenerative and/or resective therapies in the combined treatment of IP, did not obtain favorable data to justify the use of the Er:YAG laser at six months, two and four years, respectively. In addition, the wavelength (CO) of the Er:YAG laser used in the therapeutic protocol must be observed since CO greater than 2940nm promotes changes in the structuring of the implant surface. Thus, the clinical efficacy of Er:YAG laser treatment in PI was not evidenced; this can be explained by the limited protocol and sampling employed, which could compromise the results obtained by Wang *et al*. (2021).

It is known that the protein derived from the enamel matrix helps in the regeneration of periodontal tissues through cell proliferation and differentiation, and its main component responsible for this tissue neoformation is amelogenin (Hammarstrom; Heijl; Gestrelius, 1997; Hammarstrom, 1997; Bosshardt, 2008). Isehed *et al*., (2016), evaluated 26 patients who underwent surgical flap opening and decontamination of the implant surfaces either associated or not with PDME. Positive results were observed in the group treated with PDME, presenting increased bone level and a change in the microbiological composition of the site of interest. Isehed *et al*., (2018), 25 patients were treated with surgical flap opening and decontamination of the implant surfaces associated with PDME or not, observing a positive association of implant stability with the PDME group. However, the authors did not observe significant bone

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level results in the test group at 3 to 5 years follow-up. The data should be analyzed with caution due to the low number of studies in the literature about the use of PDME in treating PI, and all articles are from the same authors. However, they present promising results.

Among the limitations observed in this review study, the institutional access to the database for surveying the literature, proved to be a limiting factor, reducing the uptake of studies from the literature. In addition, the use of some natural language descriptors may have interfered in the accuracy of the bibliographic survey and the truncation of the terms, due to the lack of indexing of these descriptors in controlled language terminology records. Another point to be noted is related to the capture of data in the included studies, since some authors did not show in the writing of the article methods applied in the methodology that could influence the results of the therapeutic proposals performed, among them we can mention the pre and postoperative periods, thus compromising the qualitative assessment of this integrative review.

5 CONCLUSION

According to the established problem question, combined therapies associated with surgical techniques are effective when compared with isolated surgical therapies, thus answering the question determined in this integrative review. However, according to a qualitative analysis of the results and limitations listed in each therapy, only bone grafts associated or not with membranes and enamel matrix-derived protein presented favorable data regarding their applicability due to the peri-implant, clinical, and radiographic parameters observed, but little significant results.

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