

PLA/PGA and its co-Polymers in Alveolar Bone Regeneration. A Systematic Review

PLA/PGA y sus Copolímeros en Regeneración Ósea Alveolar. Una Revisión Sistemática

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ABSTRACT: The aim of this research was to perform a systematic review to identify the most frequent uses of PLA/PGA in alveolar bone regeneration and their results. A study was designed to answer the question: What are the most frequent uses of PLA/PLGA and their copolymers in alveolar bone regeneration?. A systematic search was done on MEDLINE, EMBASE and LILACS from April 1993 to December 2017. The search string used on MEDLINE was: (((poly(lactic acid) OR PLA) OR PLA-based copolymers) OR PLA blends) OR PLA scaffolds)) AND (((Bone Regeneration"[Mesh]) OR bone regeneration) OR guided bone regeneration). The search was complemented by a manual review of the references from the articles included. Most of the studies selected were weak and, regarding the most frequent uses of PLA/PGA, 13 studies used it as a resorbable membrane, two as an absorbable mesh, one as an absorbable screw and three as filling material. Based on our results, the authors consider that PLA/PGA requires a delicate relation between the mechanical resistance and the degradation process. PLA/PGA does not interrupt bone regeneration; however, the influence in cellular events related to bone regeneration and later osseointegration have not been identified.

KEY WORDS: poly lactic acid poly ethylene glycol, bone substitute, bone grafting

INTRODUCTION

Bone regeneration is a process that depends on several factors (Sheikh *et al.*, 2017). This process becomes more complex when bone grafts are needed to allow bone regeneration related to adequate volume and shape, necessary for orofacial rehabilitation (Sheikh *et al.*, 2015).

Biodegradable polymers have been designed to be used alone or in combination with bone substitute in some reconstructive process (Nygaard-Østby *et al.*, 2008), where polylactic acid (PLA) and polyglycolic acid (PLG) are well known materials. PLA is a biodegradable polymer obtained from lactic acid, which has osteoconductive properties and has been used in various presentations. Although its applications were originally mainly in orthopedics (Athanasίου *et al.*,

1998), for a long time it has been used in the craniofacial area for bone regeneration, as filling material in post-extraction alveolar preservation (Madan *et al.*, 2014), as resorbable membrane in the treatment of periodontal bone lesions and guided bone regeneration (Kini *et al.*, 2016; Rowe *et al.*, 2016), as resorbable internal fixation to secure bone block grafts (Mazzonetto *et al.*, 2010), as resorbable sutures (He *et al.*, 2014) and as a carrier for growth factors and bone morphogenetic proteins (BMPs) (Ma *et al.*, 2016), among others.

Nevertheless, there is limited evidence to indicate the applications and influences of PLA in craniofacial bone regeneration or the success rates of treatments performed on human beings. The aim of this study is

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to conduct a systematic review of the literature to identify the application of PLA and its copolymers in alveolar bone regeneration.

MATERIAL AND METHOD

Protocol and eligibility criteria. A systematic literature review was carried out to respond to the research question: What are the most frequent uses of PLA/PLGA and its copolymers in maxillofacial bone regeneration? The inclusion criteria for the articles were: 1) primary studies, 2) published in English, Spanish, Portuguese or French, 3) performed on humans, and 4) evaluated the use of PLA in bone regeneration. Secondary studies, studies performed on animals and those that used PLA or its copolymers for purposes other than bone regeneration were excluded. The report was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher *et al.*, 2009).

Sources of information and search strategy. A systematic search was done on MEDLINE, EMBASE and LILACS from April 1993 to December 2017. The search string used on MEDLINE was: ((((((poly(lactic acid) OR PLA) OR PLA-based copolymers) OR PLA blends) OR PLA scaffolds)) AND (((("Bone Regeneration"[Mesh]) OR bone regeneration) OR guided bone regeneration)). The search was complemented by a manual review of the references from the articles included.

Study selection and data extraction. The title and abstract of the studies identified in the search were selected independently by 2 calibrated reviewers (MP and M.P.M.). In case of differences between the reviewers, consensus was reached by discussion or in consultation with a third reviewer (SO). The reviewers were not blinded to the authors or journals.

Data were collected independently by two authors (M.P., M.P.M.) using a predefined and standardized data extraction form. A pilot test was used to homogenize criteria between reviewers. Any discrepancy was resolved by discussion or in consultation with a third reviewer (SO). Gray literature was not reviewed systematically.

Risk of bias in the individual studies. To assess the risk of bias in the studies, the Effective Public Health Practice Project's Quality Assessment Tool (Effective

Public Health Practice Project, 1998) was used, which contains six domains: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. The overall grading for each study was identified as strong when no component was weak, moderate when only one component was weak, and weak when two or more components were described as weak.

RESULTS

Study selection. The combined search identified 565 references. After excluding 60 duplicates, a review of the titles excluded 400 studies, 105 articles passed to abstract review, 27 articles were evaluated in full text, and 10 potentially relevant articles were excluded after reading the full text. After a manual review of the articles, 19 were ultimately included (Fig. 1).

Characteristics of the studies. Table 1 details the characteristics of the studies included. 2 articles were retrospective (Mau *et al.*, 2012; Rosen & Rosen, 2013)

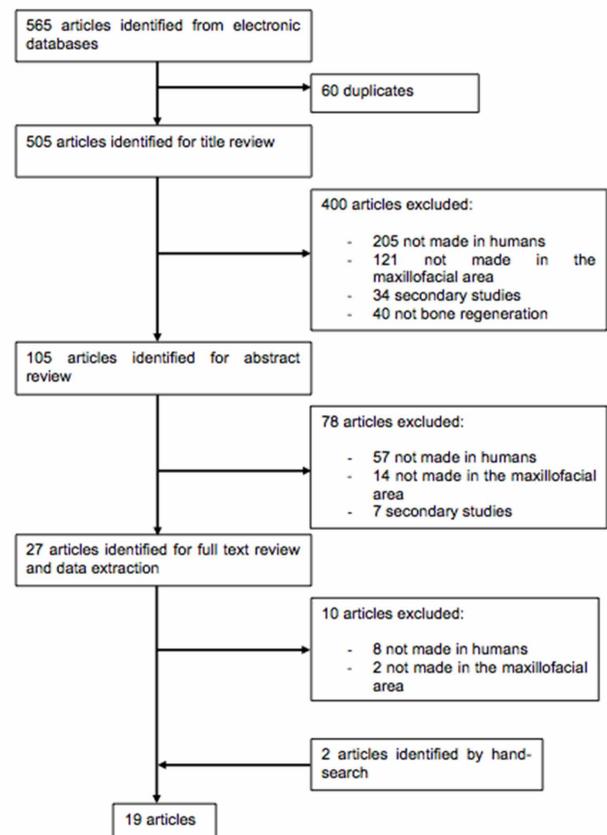


Fig. 1. Flowchart of systematic review.

Table I. Description of the articles included in this systematic review.

Author/year	Type of study	N° patients	Male	Female	Age (years) average/range	Evaluation method	Follow-up time
Simion <i>et al.</i> , 1996	Prospective	5	N/R	N/R	44 – 69	Histological	6 months
Simion <i>et al.</i> , 1997	Prospective	9	N/R	N/R	30 – 64	Clinical	8 months
Vernino <i>et al.</i> , 1998	Prospective	40	19	21	32 – 71	Retroalveolar x-ray	12 months
Trejo <i>et al.</i> , 2000	Prospective	30	11	19	30 – 55	Clinical and retroalveolar x-rays	12 months
Rosen & Reynolds, 2001	Prospective	9	7	2	32 – 81	Clinical and histological	5.7 months
Stoller <i>et al.</i> , 2001	Prospective	1	0	1	42	Clinical and histological	25 months
Serino <i>et al.</i> , 2003	Prospective	45	14	31	35 – 64	Clinical and histological	6 months
Nygaard-Østby <i>et al.</i> , 2008	Prospective	40	20	20	42 – 67	Clinical and x-ray	9 months
Serino <i>et al.</i> , 2008	Prospective	20	8	12	32 – 64	Clinical and histological	3 months
Lyons <i>et al.</i> , 2008	Prospective	29	18	11	43 - 67	Clinical	9 months
Nickles <i>et al.</i> , 2009	Prospective	16	8	8	29 – 61	Clinical	120 months
Pretzl <i>et al.</i> , 2009	Prospective	15	3	12	22 – 64	Clinical and x-ray	120 months
Matsuo <i>et al.</i> , 2010	Prospective	2	1	1	29 and 66	Clinical and CBCT	28 and 33
Mazzonetto <i>et al.</i> , 2010	Prospective	10	2	8	28 - 60	Clinical, panoramic x-ray and CBCT	6 months
Mau <i>et al.</i> , 2012	Retrospective	1	N/R	N/R	42	CBCT and retroalveolar x-ray	1 year
Baenna <i>et al.</i> , 2013	Prospective	8	N/R	N/R	N/R	CBCT	11 months
Rosen & Rosen, 2013	Retrospective	43	22	21	25-75	Clinical	23 weeks
Schneider <i>et al.</i> , 2014	Prospective	40	N/R	N/R	18 – 70	Clinical, x-ray and histological	6 months
Yagihara <i>et al.</i> , 2013	Prospective	62	41	21	12 – 78	X-rays	88.2 months

and 17 were prospective (Simion *et al.*, 1997; Vernino *et al.*, 1998; Trejo *et al.*, 2000; Rosen & Reynolds, 2001; Stoller *et al.*, 2001; Serino *et al.*, 2003, 2008; Lyons *et al.*, 2008; Nygaard-Østby *et al.*; Nickles *et al.*, 2009; Pretzl *et al.*, 2009; Matsuo *et al.*, 2010; Mazzonetto *et al.*; Rodriguez y Baena *et al.*, 2013; Schneider *et al.*, 2014; Yagihara *et al.*, 2013). The average sample size among the studies was 26 subjects, ranging between 5 and 62 subjects. In terms of the results evaluation method, one study conducted a histological analysis (Simion *et al.*, 1996), 2 studies an x-ray analysis (Vernino *et al.*; Yagihara *et al.*), 4 studies a clinical analysis (Simion *et al.*, 1997; Lyons *et al.*; Nickles *et al.*; Rodriguez y Baena *et al.*), 3 studies clinical and x-ray analyses (Nygaard-Østby *et al.*; Trejo *et al.*; Pretzl *et al.*), 4 studies clinical and histological analyses (Stoller *et al.*; Serino *et al.*, 2003, 2008), one study a clinical analysis and with cone beam computed tomography (CBCT) (Matsuo *et al.*), one study clinical, x-ray analyses and CBCT (Mazzonetto *et al.*), one study an x-ray analysis and CBCT (Mau *et al.*), one study an analysis with CBCT (Rodriguez y Baena *et*

al.) and one study clinical, x-ray and histological analyses (Schneider *et al.*).

Related to the most frequent uses of PLA and its copolymers, 13 studies used it as resorbable membrane (Nygaard-Østby *et al.*; Mau *et al.*; Simion *et al.*, 1996, 1997; Vernino *et al.*; Trejo *et al.*; Stoller *et al.*; Lyons *et al.*; Nickles *et al.*; Pretzl *et al.*; Schneider *et al.*), two as absorbable mesh (Matsuo *et al.*; Yagihara *et al.*), one as absorbable screws (Mazzonetto *et al.*) and three as filling material (Serino *et al.*, 2003, 2008; Rodriguez y Baena *et al.*) (Table II).

Risk of bias in the studies. The evaluation of the risk of bias in the studies included is reported in Figure 2. In selection bias, the first domain to be assessed, all the articles were classified as weak because they included non-probability or convenience sampling, which does not provide adequate representativity of the participants. This can cause an imbalance in some characteristics relevant to the participants like age, gender or health status, which can each influence the

Table II. Use and outcome for the use of PLA/PGA

Author/year	Use of PLA	Outcome
Simion <i>et al.</i> , 1996	Resorbable membrane in GBR, comparing it with a non-resorbable polytetrafluorethylene membrane (e-PTFE) and a control non-membrane group.	PLA membrane presented greater bone formation than in the control group, but less than in the e-PTFE group.
Simion <i>et al.</i> , 1997	Resorbable PLA/PGA membrane associated with autogenous graft in GBR to cover the bone fenestrations resulting from the installation of dental implants, comparing it to e-PTFE membrane.	88.56 % closing of the fenestration in the PLA/PGA group was obtained, with no significant differences with the e-PTFE group.
Vernino <i>et al.</i> , 1998	Resorbable membrane in the treatment of class II furcation defect.	No significant differences related to the amount of bone height, nor between the two types of membrane used.
Trejo <i>et al.</i> , 2000	Absorbable membrane (PLA/PGA) used independently or in association with DFDBA in the treatment of periodontal defects.	No significant differences between use of PLA membrane alone or associated with DFDBA
Rosen & Reynolds, 2001	Absorbable membrane plus DFDBA in the treatment of fenestrations and dehiscence after dental implant installation	10 of 11 defects achieved complete coverage of the bone defect. The histological evaluations revealed formation of viable bone.
Stoller <i>et al.</i> , 2001	Absorbable membrane in treatment class II furcation defect.	New bone formation was observed at the site of interest.
Serino <i>et al.</i> , 2003	"Fisiograft" (PLA/PGA) sponge, used as filling material in post-extraction alveolar preservation, comparing it with no-graft healing through clot formation.	After 6 months, the bone resorption was lower in the experimental group at all the sites studied compared to the control group. Histological analysis revealed mineralized, mature and well-structured bone tissue.
Nygaard-Østby <i>et al.</i> , 2008	Absorbable membrane plus autogenous graft, compared to bone graft in the treatment of periodontal bone defects	The use of a PLA membrane does not afford additional value in the treatment of periodontal bone defects with autogenous bone graft.
Serino <i>et al.</i> , 2008	Fisiograft sponge, used as filling material in post-extraction alveolar preservation, comparing it with natural healing through clot formation	After 3 months, the histological analyses showed highly mineralized and well-structured cancellous bone formation, observing a greater amount of bone in the apical portion than the cervical portion, and no particles of filling material were found in any of the samples.
Lyons <i>et al.</i> , 2008	Absorbable membrane associated with DBFA, with or without 4 % doxycycline in treatment of class II furcation defects in lower molars	There was formation of new bone; however, there were no significant differences between using or not using 4 % doxycycline associated with the membrane
Nickles <i>et al.</i> , 2009	Absorbable membrane in GTR, used in periodontal defects, comparing it to OFP (open flap debridement) therapy	They report that in both therapies there was an increase in bone tissue height, but that their analysis failed to determine statistical differences between the two groups.
Pretzl <i>et al.</i> , 2009	Absorbable membrane in GTR compared to an absorbable membrane of another material.	The authors report improvements in the levels of vertical insertion but did establish differences between the groups.
Matsuo <i>et al.</i> , 2010	Absorbable PLLA/HA mesh associated with autogenous graft used in mandibular reconstructions	The authors conclude that the PLLA/HA mesh adapts optimally to the mandible and the post-operative CBCT showed good bone quality.
Mazzonetto <i>et al.</i> , 2010	Absorbable screw for the fixation of autogenous bone grafts for the subsequent installation of dental implants.	49 absorbable PLLA screws were placed, of which 4 were lost. The authors of the work conclude that the absorbable PLLA screws do not interfere with bone healing or with the osseointegration of dental implants.
Mau <i>et al.</i> , 2012	Absorbable membrane	The authors report an adverse biological reaction resulting from the use of an absorbable PLA membrane.
Baenna <i>et al.</i> , 2013	Filling material in maxillary sinus in combination with hydroxyapatite, comparing it to DBB	The average increase in height of newly formed bone was 7.8 mm with no significant differences with the control group.
Rosen & Rosen, 2013	As an absorbable membrane in post-extraction alveolar preservation, for the later installation of dental implants, used alone or together with graft material	They presented only 4 adverse results, mainly poor bone healing in the labial area. However, in no case did it render the installation of implants impossible.
Schneider <i>et al.</i> , 2014	Absorbable membrane in GBR after the installation of dental implants, comparing it with an e-PTFE membrane.	They found no statistically significant differences between the two membranes
Yagihara <i>et al.</i> , 2013	Resorbable mesh associated with autogenous bone PCBM (particulate cancellous bone and marrow) in mandibular bone reconstructions.	Good acceptance and stability of the PLA mesh was observed and a low incidence of resorption of the bone graft.

results in their own way. In the study design, five studies were classified as strong and 14 as moderate. Although

there were controlled clinical trials, most of the studies were prospective cohorts with no control group. With

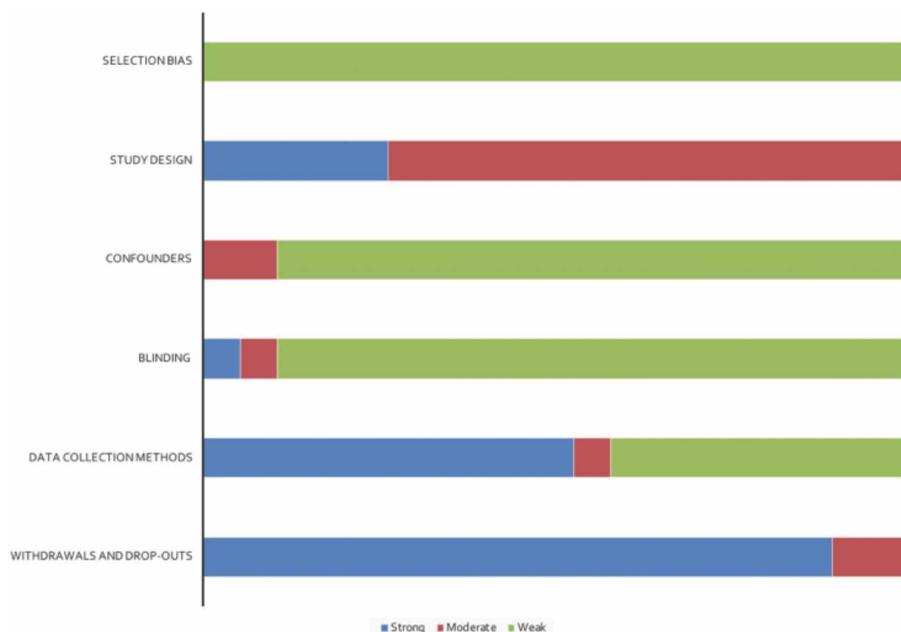


Fig. 2. Summary of risk of bias of the included studies

respect to confounder control, two were classified as moderate and 17 as weak. In terms of masking, one study was classified as strong because the patient and evaluator were blinded, one as moderate and the rest as weak. On the other hand, when analyzing the data collection methods, 10 were classified as strong, one as moderate and eight as weak, with the main strength being the use of validated methods, although not all showed high reliability. Finally, with respect to withdrawals and dropouts, this was the best evaluated domain because only in two studies were there subject dropouts; however, these did not exceed 20 % of the sample. As far as the overall evaluation is concerned, 17 studies were catalogued as weak and two as moderate (Rodríguez y Baena *et al.*; Schneider *et al.*). All the studies had at least two domains rated as weak, so they were rated as weak due to the high risk of bias they present.

DISCUSSION

PLA/PGA and its copolymers are synthetic, resorbable and highly biocompatible materials (Athanasidou *et al.*) that have been used in different bone regeneration techniques; however, there is limited information to permit an analysis of the different forms of application and their potential impact on the bone regeneration process in the maxillae.

The variability of clinical presentations and the limitations of the studies do not permit a meta-analysis of results; a large number of the studies was weak in some categories, limiting their use as solid evidence in the best application of PLA/PGA.

According to our results, the most frequent use of these materials was as resorbable membrane in different procedures, mainly in the treatment of bone defects as a result of periodontitis and in bone augmentations related to dental implants surgery. The aim of this application was to allow the

immobilization of the bone graft or bone substitute used, and to serve as a barrier to avoid the growth of connective tissue inside the bone substitute (Lee & Kim, 2014).

For PLA / PGA related to implant dentistry, was performed the installation of dental implants in atrophic sites, and then installation of particulate xenograft covered by a PLGA membrane for stability of the filling and was compared to cases treated by non-absorbable ePTFE membrane (Schneider *et al.*). After 6 months follow-up, survival rate of the dental implants in both groups was 100 % and no differences was observed. This is consistent with other authors (Arunjaroen suk *et al.*, 2018), who compared the use of a PLA / PGA membrane as an experimental group and a collagen membrane as a control in bone augmentation during dental implants installation, also reporting a 100 % survival of the implants in both groups.

Resorbable membrane with no resorption for 4 to 6 weeks, could be beneficial for bone regeneration, as was demonstrated in an experimental study on dogs (Lekholm *et al.*, 1993); biodegradable implies the absence of secondary surgery for its removal. The few studies that reported the characteristics of these membranes indicated they were porous for attracting, trapping and retaining the fibroblasts and epithelial cells while maintaining the space for the growth of new bone and periodontal tissue (Barbeck *et al.*, 2015).

Simion *et al.* (1996) conducted a study in humans and compared resorbable PLA/PGA

membranes and non-resorbable polytetrafluorethylene (e-PTFE) membranes in the treatment of bone defects around implants installed immediately after extraction, without bone graft. After six months, they found significant differences in the amount of newly formed bone, being greater in the group where non-resorbable e-PTFE membrane was used. They indicated the rapid degradation time as the main cause of failure of the PLA/PGA membranes.

Simion *et al.* (1997), in a study of similar characteristics, found no statistically significant differences when using a resorbable or non-resorbable membrane after six months of follow-up. Similarly, using both types of membrane in the covering of periodontal bone defects associated with autogenous bone graft, other authors (Nygaard-Østby *et al.*) found no significant differences in a comparison of the two membranes.

Another uses of PLA/PGA and its copolymers described in the maxillomandibular area was as filling in post-extraction alveolar preservation, a procedure performed to preserve or avoid large bone resorptions of the alveolar process after a tooth extraction, and thus achieve a subsequent successful installation of a dental implant (Scheyer *et al.*, 2016). A great variety of materials has been used as filling in post-extraction alveoli with varying rates of success (Iocca *et al.*, 2017). On the use of PLA/PGA in this therapy, Serino *et al.* (2003) created a PLA/PGLA sponge model that was applied in post-extraction alveoli. After six months of follow-up, it was noted that the loss of bone height was greater in the alveoli that were not treated with bone graft or filling than those treated with the application of the post-extraction sponge.

In another similar study, Serino *et al.* (2008) observed that in biopsies in the experimental group, there was intense osteoblastic activity and the presence of mature bone tissue for the most part, without observing residual particles of the PLA/PGLA filling; by contrast, a significant presence of connective tissue and immature bone tissue was observed in the control group. The authors reported that the degradation of PLA/PGA involves hydrolytic degradation (Cutright *et al.*, 1974), whereas other materials like b-TCP are eliminated faster by remodeling-resorption than the PLA/PGA (evaluated six weeks after implantation) (Draenert *et al.*, 2013); hence, the greater maintenance of the PLA could contribute to greater maintenance of the post-extraction anatomy.

Another PLA-based application is the manufacture of osteosynthesis screws. Mazzonetto *et al.* reported the application of osteosynthesis screws for internal fixation of autogenous bone blocks extracted from the iliac crest, thereby avoiding the subsequent removal of the osteosynthesis for the installation of dental implants. The mechanical characteristics of these PLA/PGA screws have been evaluated for more than 15 years in the maxillofacial surgery literature, describing good results, similar to those obtained by titanium elements (Rodríguez-Chessa *et al.*, 2014). In maxillofacial surgery, these osteosynthesis systems have been used in maxillofacial traumatology, orthognathic surgery and craniofacial surgery without presenting any changes in the bone repair mechanism of fractures or osteotomies (Ueki *et al.*, 2012).

The complications associated with PLA/PGA screws are relatively low (Yang *et al.*, 2013); a probable limitation in this reconstructive technique is that a screw guide is required prior to the installation of the screws, which can limit the use of compressive techniques between the bone graft and the native bone.

Based on our results, the authors estimate that the use of PLA/PGA requires a delicate relation between the mechanical resistance and the degradation process, so that the different presentations must contain differences in the composition of the products. A screw, for example, must be less flexible than a membrane or a sponge; thus, the elimination of the material must maintain a relationship with bone regeneration so that the new formation in a bone defect or in the osseointegration process is not interrupted. The results of this study show that the application of PLA does not interrupt bone regeneration; however, the influence of PLA on the physiological events of regeneration and osseointegration in the long term must be identified. New research studies with adequate methodology are necessities for an evidence based decision.

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RESUMEN: El objetivo de esta revisión fue realizar una revisión sistemática de la literatura para identificar los usos más frecuentes de PLA/PGA en regeneración ósea en área maxilofacial y sus resultados. Se diseñó un estudio para responder a la pregunta: ¿Cuáles son los usos más frecuentes de PLA/PLGA y sus copolímeros en regeneración ósea

en el sector maxilofacial?. Los estudios seleccionados fueron en su mayoría débiles y sobre los usos más frecuentes de PLA/PGA, 13 estudios lo utilizaron como membrana reabsorbible, 2 estudios como malla absorbible, un estudio como tornillo absorbible y 3 estudios como material de relleno. En base a nuestros resultados, los autores estiman que PLA/PGA requiere una delicada relación entre la resistencia mecánica que ofrece y la degradación que se produce; PLA/PGA no interrumpe la regeneración ósea, sin embargo, no se ha identificado la potencialidad o influencia que presenta en los eventos celulares de la regeneración y posterior oseointegración.

PALABRAS CLAVE: PLA/PGA, sustituto óseo, injerto óseo.

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