

# USE OF PLA-PGA (COPOLYMERISED POLYLACTIC/POLYGLYCOLIC ACIDS) AS A BONE FILLER: CLINICAL EXPERIENCE AND HISTOLOGIC STUDY OF A CASE

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Running head: PLA-PGA AS A BONE FILLER

## Abstract

This study describes our preliminary experience on the use of a new polylactic/polyglycolic copolymer used as a bone filler. In 30 post-extraction and periodontal cases the synthetic material proved to be extremely easy to handle thanks to the various forms available (sponge, powder and gel) which adapt well to the various cases which require filling with subsequent formation of new bone.

The clinical and radiographic show that the new biomaterial is biocompatible, non-allergenic and did not produce an inflammatory response.

In one clinical case the histological findings demonstrate that, on completion of healing, the biopolymer is totally replaced by trabecular bone; between the trabeculae it is possible to observe spaces containing adipose cells and vascular cells, indicating the formation of medulla ossium.

These results were confirmed by electronic microscopy.

## Key words

Bone defects, osseous repair, bone filler

## Introduction

Current periodontal surgery sometimes requires the use of bone grafts (autologous and/or allogenic) to provide structural support during healing of the bone and to replace damaged or diseased tissue. In the case of allografts, there is however a risk of cross infections (hepatitis, BSE, etc.), while autologous grafts, particularly if extensive, are associated with a risk of surgical problems and post-operative complications at the donor site.

In light of the above, synthetic materials are used with increasing frequency in clinical practice. The literature describes a vast range of fillers used to repair bone defects and synthetic bioabsorbable polymers represent one of the principal innovations in the biomaterial sector (Ashman 1992, Ashman 1993a, Ashman 1993b, Ewers & Lieb-Skowron 1990, Kulkarny et al. 1971).

Among these, polylactic acid (PLA) and polyglycolic acid (PGA) have been used in the

orthopaedic field and in maxillofacial surgery for more than a decade, proving highly effective in osteosynthesis studies (Bos et al. 1989, Desilets et al. 1990, Giudice 1993, Hollinger & Schmitz 1987, Majola 1991, Manninen et al. 1992, Miettinen et al. 1992, Paivarinta et al. 1993, Rehm et al. 1994, Suuronen 1993, Thaller et al. 1992, Tschkaloff et al. 1993, Vasenius et al. 1990).

In dentistry, surgical sutures and absorbable membranes in PGA and/or PLA acids have been available for some time for use in guided tissue regeneration (Robert et al. 1993, Robert & Frank 1994). However, only in recent years have absorbable synthetic biopolymers been used as bone fillers in periodontology, proving effective stimulants to bone regeneration in some cases (Lundgren et al. 1992, Miyamoto & Takaoka 1993, Winet & Hollinger 1993).

One of the main advantages of these polymers is their complete biocompatibility: PLA degrades into lactic acid which is then broken down into water and carbon dioxide in

the Krebs cycle (the Krebs cycle is a chain of biochemical reactions normally present in the organism in which energy is produced through the use of glucide precursors), while PGA, on the other hand, is broken down through a specific enzyme process (Bos et al. 1989a, Bos et al. 1989b, Bos et al. 1991, Cutright & Hunsuck 1971, Leenslang et al. 1987). In 1994, a new biomaterial (F) appeared on the Italian market, consisting of a copolymerised polylactic/polyglycolic acid (PLA-PGA) and is destined for use as a synthetic bone filler in oral surgery.

This copolymer has a spongy open-cell structure enabling it to be colonised by the osteoblasts. The time taken for it to be reabsorbed depends on the relative percentage of the components and it presents no risks from a biological point of view, being synthetic and not a human or animal derivative.

It is available in **sponge**, **powder** and **gel** form and can be used in dentistry as a filler according to the operator's needs in relation to the characteristics of the utilisation site.

The ratio of PLA to PGA is 50/50 and different formulas are available depending on the excipients used.

The **sponge** is produced through the lyophilisation of PLA-PGA and dextran. Of considerable consistency, the sponge is hydrated if necessary and then softened using physiological solution or blood and inserted in the recipient site, without being compacted.

The **powder** is obtained by pulverisation of the sponge. Powder and sponge are normally used together to fill infra-bony pouches, extraction sockets or other bone defects where the material can be held in place via a flap.

The **gel** is a new formula for synthetic filler material and is especially suitable for filling irregular cavities where a flap is unable to close the defect completely. This is due to the greater intrinsic stability of the gel inside the recipient site. The gel is injected directly into the defect using the syringe provided.

## Our clinical experience

In the light of the application potential described above, the new biomaterial was

assessed at the Periodontology Department of the University of Bologna in thirty clinical cases where the common aim was to obtain new bone deposits.

Although a rigid experimental protocol was not adopted, these first thirty cases represented a clinical investigation, in particular into the flexibility and ease of handling of the three forms of the product and the results obtained. The study involved 17 males and 13 females aged between 29 and 66:

- 18 undergoing periodontal surgery: 2 associated with the use of resorbable membrane (Paroguide); 1 with the use of non-resorbable membrane (Gore);
- 10 undergoing post-extraction filling: 1 associated with the use of resorbable membrane (Vycril);
- 2 undergoing implant surgery: 1 with use of resorbable membrane (Paroguide); 1 with the use of non-resorbable membrane (Gore).

In all these cases the defect was filled with an appropriate quantity of Fisiograft, choosing the powder formulation in 9% of the cases, the sponge formulation in 27% and the gel formulation in 64%; in some cases the various formulations were used together.

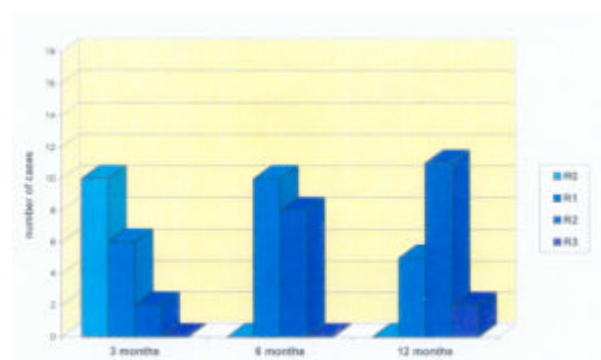
Each case was photographed and monitored over a period of time both from a clinical point of view and via intraoral radiographs. Within the limits due to the possibility of comparing radiographs taken at different times but with a standardised technique, the radiological images were used to indicate the degree of filling of the defect as:

R=0 no filling

R=1 filling less than 50%

R=2 filling more than 50%

R=3 total filling.



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Figure 1 - Variation in the filling of the bone defect from the radiographs taken at 3, 6 and 12 months, in the cases undergoing periodontal surgery. R=0 No Filling, R=1 Filling less than 50%, R=2 Filling more than 50%, R=3 Total filling

Figures 1 and 2 show the results obtained: progressively higher bone filling can be noted in the post-extraction cases, in any case satisfactory in both clinical cases.

The state of physiological reaction present immediately after the operation rapidly regressed over the subsequent days, without any patient being prescribed specific anti-inflammatory treatment. There were no cases of inflammatory relapse after the week following the operation.

As confirmation of the favourable results obtained in this study, the deposition of new bone was assessed objectively in a number of cases through histologic examination of core samples taken during implant operations.

As an example, one of these cases is described below.

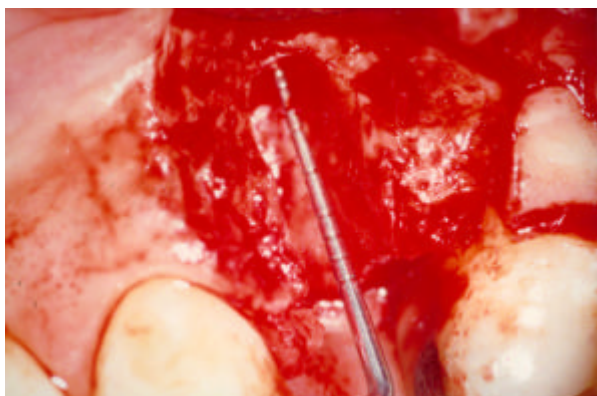


Figure 3 - Cavity of the upper left premolar with complete absence of the vestibular wall

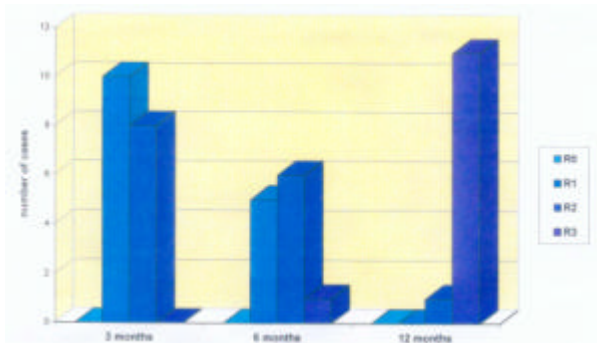


Figure 2 - Variation in the filling of the bone defect from the radiographs taken at 3, 6 and 12 months, in the

cases undergoing extraction (10 cases) and implants (2 cases)

## Case report

The observations relate to a particularly compromised left upper premolar in a 45-year-old female patient.

This tooth had already been unsuccessfully treated endodontically with a retrograde and orthograde approach. X-ray examination showed a periapical osteolysis with a diameter of about 5 mm.

It was decided to extract the tooth and insert an appropriate quantity of Fisiograft into the cavity. The sponge formula was chosen for its compact consistency, making it suitable for filling large cavities.

A muco-periosteum flap was created enabling the biomaterial used as a bone filler to be protected and retained in place.

The following procedures were carried out at the same time as the extraction:

1. curettage of the cavity where the vestibular wall was found to be completely lacking (fig. 3);
2. creation of inductive perforations to encourage new bone deposition;
3. positioning of sponge-type Fisiograft suitably hydrated with sterile physiological solution (fig. 4);

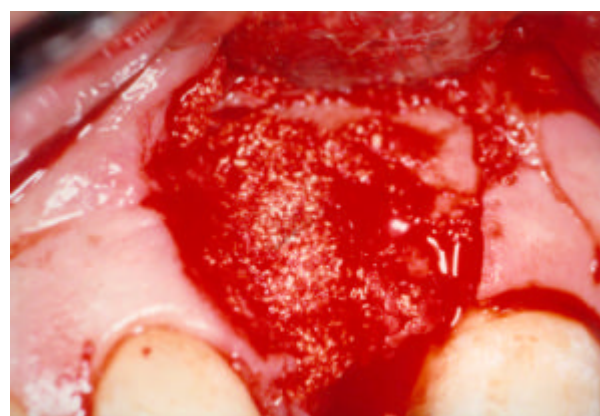


Figure 4 - Positioning of sponge-type Fisiograft after appropriate hydration

4. positioning on top of this of a absorbable polyglycolic membrane (Vycril mesh),

5. covering of the cavity with a muco-gingival flap and stabilisation with loop sutures;
6. a first X-ray examination of the site immediately after positioning of the biomaterial (fig. 5a). The alveolus presents with a maximum level of radio transparency due to the fact that the biomaterial itself is not radiopaque;

The sutures were removed 7 days after the operation.

X-ray controls were carried out at 4.5 months and at 8 months (fig. 5b and 5c). The radiograph taken at 4.5 months shows neotrabeolum bone which appears to be greater at the apical portion. In the radiograph taken at 8 months the formation of the neoformed bone is almost completed and it has progressed to the coronal region. These radiograph sequences show progressive opacification of the graft site which are common findings for the healing process involving a healthy post extraction alveolus. In this case there were only three residual walls, which in the absence of the biomaterial would have resulted in a drastic reduction of the final bucco-lingual width. Instead the results appear to be optimal for the introduction of a prosthetic implant.

Nine months after the operation an access flap was cut exposing the newly formed mineralised tissue, identical to bone tissue (fig. 6). During the operation, a core sample of tissue was taken (suitably fixed with buffered formalin) and sent for histologic examination to confirm the clinical observation.



Figure 5a - Intra-oral X-ray of the site after positioning of the biomaterial. The alveolus presents with a maximum level of radio transparency this is due to the fact that the biomaterial is not radiopaque

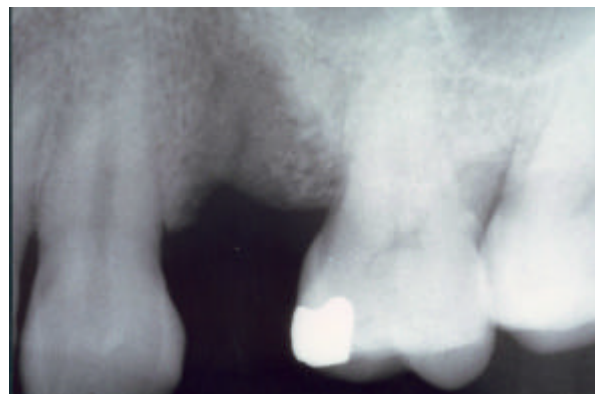


Figure 5b - Intra-oral X-ray of the site after 4 and a half months. The radiograph shows neotrabeolum bone which appears to be greater at the apical portion.

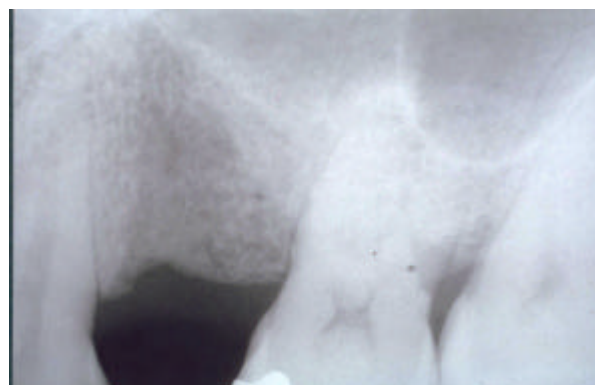


Figure 5c - Intra-oral X-ray of the site after 8 months. Here the formation of the neoformed bone is almost completed and it has progressed to the coronal region.

### ***Histologic examination***

On biopsy, the material removed appeared to consist of well-mineralised lamellar bone with the characteristics of normal alveolar bone. Internal spaces were observed containing connective tissue and blood vessels (fig. 7) (evidence of the presence of active bone tissue repair and reconstruction phenomena).



Figure 6 - Exposure of the newly formed tissue after 9 months: the presence of a newly formed layer of bone is evident, suitable for implant

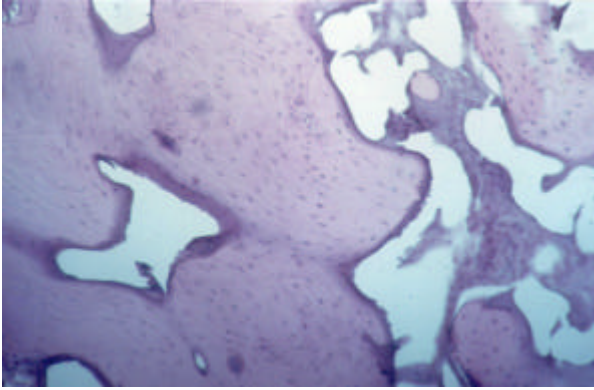
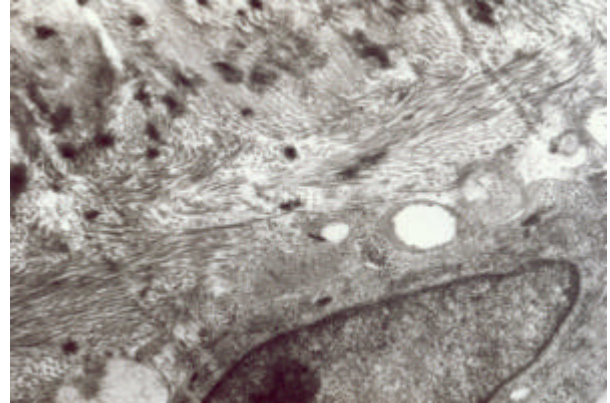
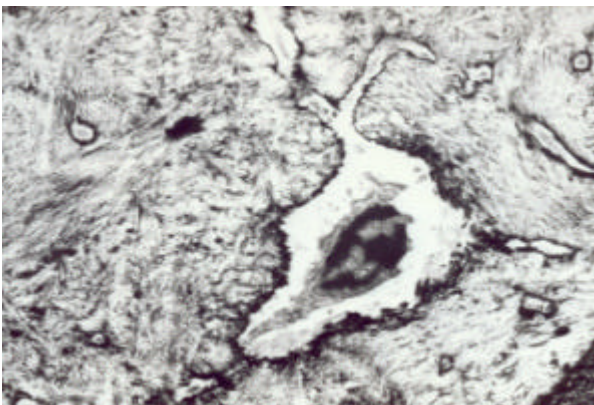


Figure 7.- Histological analysis of the biopsy specimen showed well-mineralised lamellar bone, with the characteristics of normal alveolar bone. Internal spaces can be seen containing connective tissue and blood vessels.

As confirmation of the normal anatomic situation, there were numerous osteons present in the bone tissue structure consisting of concentric lamellae arranged around the haversian canals. Between these, were numerous bone cavities containing osteocytes. In a number of areas, the presence of interstitial lamellae, the residue of earlier generations of osteocytes, indicate that a previous reorganisation of bone tissue had already taken place.

Microscopic observation showed no trace of the implanted material, inflammatory infiltrate or foreign-body granulomas which would have demonstrated the incompatibility of the material.



Figures 8 and 9 At electron microscopy the haversian canals are lined with bone progenitor cells. The ground substance contains bundles of collagen fibrils with regular alternating light and dark bands. They are parallel to each other within the individual lamellae, but neighbouring lamellae have different orientations. The specimen appears to be well mineralised, as shown by the presence of numerous hydroxyapatite crystals in the structure of the collagen fibre bundles, and cellularised by elements identifiable as osteocytes (magnification fig. 8 x 9,000; fig. 9 x 6,000).

The examination concentrated in particular on ascertaining the absence of the lymphocytes, macrophages, plasma cells, giant cells and mast cells always present in cases of chronic inflammation.

Fine structure electron microscope analysis further confirmed the optical microscope observations (fig. 8 and 9).

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## Discussion

The synthetic copolymer used in these cases proved to be extremely easy to handle as a result of the various forms available (sponge, powder and gel) which easily adapt to the various cases requiring use of a filler with subsequent formation of new bone.

The use of Fisiograft with resorbable membranes was found to give optimum results.

Clinical and instrumental data obtained from these cases showed that the new biomaterial was biocompatible, non-allergenic and did not produce an inflammatory response, confirming the data contained in literature (Hollinger 1983, Meikle et al. 1994, Vert et al. 1994, Winet & Hollinger 1993).

It should be emphasised that due to its synthetic origin, there is a complete absence of biological risk.

The histologic findings showed that the copolymer remained in the site of the graft until completion of the natural healing processes. At the same time it is penetrated and gradually and totally replaced by trabecular bone.

Between the trabeculae, there are spaces containing adipose and vascular cells indicating the formation of medulla ossium (Schakenraad & Dijkstra 1991, Winet & Hollinger 1993). Previous studies in animals and humans indicate that total absorption occurs about four months after placement of the graft (Leghissa et al. 1997, Saitoh et al. 1994) with a histologic profile comparable to that noted in the clinical case described above.

One of the uses which appears most promising in the future is the possibility of adding bone growth factors to the polylactic/polyglycolic copolymer. Initial experiments (Miyamoto et al. 1992, Miyamoto & Takaoka 1993, Miyamoto et al. 1993) show that the copolymer serves as an excellent carrier for these factors.

Our experience gives grounds for optimism regarding the future of this synthetic bone replacement biomaterial, which demonstrated osteoconductivity, considerable practical flexibility and excellent biocompatibility. The results obtained represent a valid premise for further studies to confirm the product's efficiency in stimulating bone growth.

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