Histometric Analysis of Bone Repair in Bone-Implant Interface Using a Polylactic/Polyglycolic Acid Copolymer Associated With Implants in Rabbit Tibia

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The purpose of this study was to evaluate the association of the combination of polylactic/polyglycolic acid around implants installed with and without primary stability through the histometric analysis of bone-implant interface. We used male rabbits, each of which received 2 titanium implants in each tibial metaphysis. The animals were divided into 4 groups: control with primary stability (CPS), control without primary stability (C), polymer with primary stability (PPS), and polymer without primary stability (P). Euthanasia was performed at postoperative days 40 and 90. The pieces were embedded in resin, sectioned, scraped, and stained with alizarin red and Stevenel blue. Histometric analysis evaluated the linear extension of contact between the bone and implant surface on the implant collar (CIC) and contact between the bone and implant surface on the first thread (CFT). Also evaluated was the area of newly formed bone (ANB) in the first thread. The results showed that there was new bone formation in all groups and during all periods. At 40 days, the ANB was higher in the PPS group than in the P group ($P < .001$); the CFT was statistically higher in the CPS group than the PPS group ($P < .001$) and was higher in the CPS group than the C group ($P < .001$). At 40 and 90 days, the CIC was higher in the P group than in the C group ($P < .001$). In conclusion, the copolymer had biocompatibility, enhanced bone healing, and presented osteoconductive properties, thus raising the contact between bone and implant, even without primary stability.

**Key Words:** dental implants, bone substitutes, osseointegration, bone regeneration.

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**INTRODUCTION**

The use of dental implants represents an important treatment for edentulous patients (partial or total); however, success depends on intimate contact of bone tissue with the implant, that is, bone integration. The implant remains in the receptor because of the presence of primary stability, and this has been identified as a prerequisite for...
obtaining osseointegration. Bone density, proportion of cortical and medullar bone, quality of bone tissue, presence of dental alveoli after tooth extraction, and inadequate preparation of the receptor are factors that may interfere in the primary implant stability.  

Bone tissue has a high capacity for repair and regeneration, and its original structure and function may be completely restored. However, in some situations, because of the size of the bone defect, the bone tissue does not regenerate completely. In an attempt to promote primary implant stability, especially in cases of poor-quality bone, clinicians use bone grafts as well as allogeneic, xenogenous, and, more recently, synthetic bone substitutes. To avoid or minimize the limitations of autogenous bone grafts, especially considering their limited availability for large reconstructions and surgical morbidity, researchers have had good results using biomaterials or bone substitutes. Other researchers have reported that polymeric materials have the advantages of biocompatibility, good mechanical properties, easy handling and inhibition of the infectious and immunologic complications reported with materials of biological origin. Moreover, these materials are bioabsorbable through metabolic hydrolysis, so patients do not have to undergo surgery to remove the device.

The main polymeric materials currently studied are polylactic acid (PLA) and polyglycolic acid (PGA), alone or as copolymers. Rabbit studies have shown that PGA is degraded more quickly (2 months) than PLA (12 months). It is also known that the hydrolysis of copolymers of PLA/PGA in solid form results in the release of lactic acid monomers, which are oxidized to form pyruvic acid. Rimondini et al analyzed bone repair after implantation of a copolymer of PLA/PGA (50:50 proportion) used as bone substitute and concluded that this copolymer, dispersed in a hydrosoluble matrix, is osteoconductive in critical bone defects. Several studies have shown beneficial effects of these copolymers in animals and humans, focusing on their osseoconductive properties because they work as a frame for the replacement of the extracellular matrix.  

Given the importance of primary implant stability in biomechanics and subsequent osseointegration, and considering the natural or induced anatomic changes in bone tissue, the combination of resorbable biomaterials at the site of implant installation becomes important. Among them is the copolymer of PLA/PGA, which could contribute to the temporary stability of implants by modifying the biomechanics of the bone-implant interface and could promote bone conduction.  

The purpose of this study was to evaluate the association of the PLA/PGA copolymer around dental implants installed with or without primary stability through the histometric analysis of the bone-implant interface.

**Materials and Methods**

We used 10 white male rabbits (New Zealand, *albinus* variation) aged 5 months and weighing 3 to 4 kg. The animals were kept in individual cages and fed a standard diet of solid food (Procoelho, Primor, São Paulo, Brazil) and water ad libitum. The study, submitted to the Ethics Committee on Animal Experiments of the Faculty of Dentistry of Araçatuba-UNESP, was approved under protocol number 2007/07948–9.

**Experimental Surgery**

Food was withheld from the rabbits for 8 hours before the surgery, and rabbits were sedated by a combination of 50 mg of intramuscular ketamine (Vetaset, Fort Dodge Animal Health Ltd, Campinas, São Paulo, Brazil) and 5 mg/kg xylazine hydrochloride (Dopaser, Laboratory Calier of Brazil Ltd, Osasco, São Paulo, Brazil) and received mepivacaine hydrochloride (0.3 mL/kg, Scandicaíne 2% with epinephrine 1:100 000, Septodont, Saint-Maur-des-Fossés, France) as local anesthesia and hemostasis of the operative field.

After the rabbits were sedated, trichotomy was performed in the medial portion of the right tibia. Polyvinylpyrrolidone-iodine detergent (10% PVP-I, Rioquímica, São Paulo, Brazil) and 5 mg/kg xylazine hydrochloride (Dopaser, Laboratory Calier of Brazil Ltd, Osasco, São Paulo, Brazil) and received mepivacaine hydrochloride (0.3 mL/kg, Scandicaíne 2% with epinephrine 1:100 000, Septodont, Saint-Maur-des-Fossés, France) as local anesthesia and hemostasis of the operative field.

After the rabbits were sedated, trichotomy was performed in the medial portion of the right tibia. Polyvinylpyrrolidone-iodine detergent (10% PVP-I, Rioquímica, São José do Rio Preto, Brazil), associated with topical PVP-I, was applied as an antiseptic to the region to be incised.

Using a #15 blade (Feather Industries Ltd, Tokyo, Japan) an incision about 3 cm long was made in the tibial metaphysic region (left and right). The bone tissue was then exposed using periosteal retractors to receive implants.

Next, we installed 40 titanium implants that had been surface treated by acid etching and sandblasting (SLA, Connection, São Paulo, Brazil). These
implants, which have a square implant collar, were 2.6 mm in diameter and 6.0 mm in height and were sterilized by gamma rays.

Each rabbit received 4 implants, 2 in each tibial metaphysis; a distance of approximately 10 mm was kept between them. In the right tibia, the implants were installed with primary stability, and in the left tibia, they were installed without stability, creating 4 experimental groups:

**Control with primary stability (CPS):** The implants were installed in the bone defect after osteotomy of 2.0 mm in diameter and 6.0 mm deep, were filled only with blood clot, and had primary stability.

**Control without primary stability (C):** The implants were installed in the bone defect after osteotomy of 3.0 mm in diameter and 6.0 mm deep, were filled only with blood clot, and had primary stability.

**Polymer with primary stability (PPS):** The implants were installed after osteotomy of 2.0 mm in diameter and 6.0 mm deep, were associated with the copolymer of PLA (70%) and PGA (30%) in a 1:1 proportion (VETEC Fine Chemicals Ltd, Duque de Caxias, RJ, Brazil), were heated between 100 and 150°C to gel consistency, and had primary stability.

**Polymer without primary stability (P):** The implants were installed after osteotomy of 3.0 mm in diameter and 6.0 mm deep, were associated with the copolymer of PLA (70%) and PGA (30%) in a 1:1 proportion (VETEC Fine Chemicals Ltd), were heated between 100 and 150°C to gel consistency, and did not have primary stability.

The copolymer was prepared by mixing PLA (70%) and PGA (30%) (in the proportion of 1:1) and then adding this mixture to the polyvinyl alcohol, heating the mixture to a temperature between 100 and 150°C, until the liquid reached the consistency of a gel after polymerization.

We used an electric motor with a final speed of 1600 rpm to prepare bone defects at a 16:1 reduction contra-angle (Kavo, Santa Catarina, Brazil). Preparation of receptors began with a cutter to delimit the location of the implants and break the cortical bone. Then we used the helical cutter at 2.0 mm for the groups in which the implants were installed with primary stability (CPS and PPS). In groups C and P, we used the same sequence of cutters outlined earlier, adding a pilot of 2.0 mm/3.0 mm and, finally, the helical cutter 3.0 mm (Connection, São Paulo, Brazil) was used sequentially along with irrigation with a solution of sodium chloride 0.9% (Darrow, Rio de Janeiro, Brazil) during the preparation. In the PPS and P groups, the implants were surrounded by the copolymer; the copolymer was also placed on the surgical defect before the implant was installed. The defects involved only the superior cortical bone (monocortical bone).

Tissues were sutured in planes using absorbable thread (Poligalactina 910 - Vycril 4.0, Ethicon, Johnson Products, São Jose dos Campos, Brazil) with continuous stitches in the deep plane and monofilament (Nylon 5.0, Ethicon, Johnson) with interrupted stitches in the more external plane.

In the immediate postoperative period, the rabbits received intramuscular pentabiotic (0.1 mL/kg, Fort Dodge Animal Health Ltd), repeated after 5 days. They also received dipirone (1 mg/kg, Arisont Chemical and Pharmaceutical Industries Ltd, São Paulo, Brazil) totaling 3 doses. Euthanasia was performed at 40 and 90 days after surgery, 5 rabbits per period, by anesthetic overdose.

There were no complications in the transsurgical and postoperative periods. The animals showed no signs of infection at the incision site.

**Histologic and Histometric Analysis**

After euthanasia, the right and left tibial metaphyses were removed and margins were reduced about 1 cm to the fullest extent of the defects. They were fixed in buffered formalin 10% (Analytical Reagents, Dynamics Odonto-Hospitalar Ltda, Guarulhos, SP, Brazil) for 48 hours and washed in water for 24 hours. After fixation, the pieces went through the dehydration stage via a gradually increasing sequence of alcohols—70, 90, 95, and 100; the solution was changed every 3 days. Dehydrated parts were placed in an orbital shaker (Kline CT - 150, Cientec - Laboratory Equipment, Piracicaba, SP, Brazil) every day for 4 hours.

After dehydration, the pieces were immersed in acetone (Labsynth Products Laboratories Ltda, Diadema, SP, Brazil) for 24 hours and then placed in a solution of acetone and slow polymethylmethacrylate (PMMAL; Classico, Articles Dental Classic, São Paulo, SP, Brazil) at a ratio of 1:1. Subsequently, the pieces were immersed in 3 baths of PMMAL, and the catalyst benzoyl peroxide (1% Riedel - De
Haen AG, Seelze-Hannover, Germany) was added to the last bath.

The last bath (PMMAL and catalyst) was performed with the pieces placed in glass jars with lids and kept at room temperature for about 1 week so that the resin cured. After polymerization, the blocks with the pieces were initially bisected at the mesiodistal place using a floppy-sided diamond disc (KG Sorensen, number 7020, São Paulo, Brazil).

Manual progressive wear was applied with wet sandpaper granulation 3M 220, 400, 600, and 800 (3M Brazil, Sorocaba, SP, Brazil) under fluorescent light, gradually up to a thickness of 100 mm in diameter in the longitudinal implants.

The histologic sections were fixed on glass slides using epoxy adhesive (Araldite Epoxy Systems for Lamination, Huntsman, MAXEPOX, Santo Amaro, São Paulo, Brazil) and stained with alizarin red and Stevenel blue. Coverslips were mounted with Permount (Fisher Chemical, Fisher Scientific, Waltham, Mass). After fixing the coverslips, the edges were insulated with enamel to prevent the depletion of oil, thereby preventing the piece from drying out.

The images were captured using a conventional optical microscope (Leica Microsystems Aristoplan Leitz, Bensheim, Germany) coupled with a digital camera for image capture (Leica DFC 300FX, Leica Microsystems, Heerbrugg, Switzerland) and connected to a computer with a software analyzer for scanned images (Leica Camera Software Box, Leica Imaging Manager-IM50 Software).

For the histometric analysis, we used the ImageLab 2000 program, version 2.4 (Diracom BioInformática, Vargem Grande do Sul, São Paulo, Brazil), and calculated the linear extent of contact between the newly formed bone (ANB) tissue (stained with alizarin red) and the implant surface on the implant collar and the on the first thread and in the area of ANB on the first thread on each side of the implant (located in the cortical bone) because of the anatomy of the receptor (wide medullar space), similar to the method of Johansson et al.25

The data were converted to percentages and compared using analysis of variance (ANOVA) and Tukey test for multiple comparisons between groups and time periods, adopting a significance level of 5%. Mean values of ANB, contact between the bone and implant surface on the implant collar (CIC), and contact between the bone and implant surface on the first thread (CFT) were analyzed.

**RESULTS**

**Clinical Analysis**

After reopening the tibia to removing the pieces, the implants were observed to be stable at 40 and 90 days, with the newly formed bone covering the implant collar (Figure 1). Implants in the primary stability groups presented in a three-dimensional position closer to the installation position, and the groups without stability presented in a prone position compared with the initial installation. In the groups without primary stability, the placement of implants from P group was less inclined than the placement of implants from the C group (Figure 1).

In groups where the implants were installed with primary stability, there was no clinical change in the position of the implants after osseointegration. In the groups where the implants were installed without any primary stability, during the reopening and exposure of the implants, it was found that they were a little inclined (or angulated) because they were not stability. This small tilt (or angulation), observed clinically in groups of implants placed without primary stability, was lower when these implants were associated with the copolymer of PLA/PGA. The copolymer fills up the spaces between the implant and the surgical site, which helps maintain the primary position of implants installed without stability by producing a gel consistency.

**Histologic and Histometric Analysis**

The qualitative results show that there was new bone formation in all groups and during all periods. In groups with stable implants (CPS and PPS), mature newly formed bone tissue (stained with alizarin red) was observed, predominantly in contact with the implant collar, at both time periods (Figures 2a through 5).

The presence of mature bone tissue throughout most of this area was observed because the implant collar was located in the cortical bone, where there was higher bone formation (Figures 2a and 3a). At the implant threads, the bone formation was lower because these areas are located wholly or partially within the medullary canal, where bone formation is reduced. Adjacent to the newly formed bone, we observed the presence of fibrous connective tissue (stained Stevenel blue) in both groups and periods (Figures 2b, 3b, and 4).
In the group with the PLA/PGA copolymer (PPS group), at 40 days the presence of the copolymer was observed mainly on the threads, that is, near the marrow canal. At this area, connective tissue and a high presence of cells and numerous osteoblasts were observed around the remainder of the polymer, which was being degraded and replaced by the adjacent collagenous matrix (Figure 4b). At 90 days there was less copolymer in the area of the threads of the implant (medullary area) (Figure 5b).

In groups where the implant was not stable (C and P groups), we observed the presence of mature bone tissue in contact with the implant collar (cortical bone) in the 2 studied periods (40 and 90 days).

For comparison between groups and periods, ANOVA was applied for the 3 criteria for analysis (ANB, CFT, and CIC), and there was a statistically significant difference between groups for each criterion ($P < .001$). Therefore, the Tukey test was applied for multiple comparisons between groups and periods to verify in which groups these differences were present ($P = .05$).

Comparisons between the groups with primary stability (CPS and PPS groups) and without primary stability (C and P groups) showed that, after 40 days, the ANB was higher in the PPS group than in the P group ($P < .001$), and CFT was higher in the CPS group than in the C and PPS groups ($P < .001$), that is, the lack of primary stability and the presence of the copolymer delayed the bone-formation process.

In CIC there was a statistically significant difference in the P group compared with the C group at 40 days ($P = .03$) and 90 days ($P < .001$).

Tables 1, 2, and 3 show the mean, SD, and maximum and minimum values for the different
FIGURES 3–5. **Figure 3.** (a) At 90 days, the bone tissue also filled the areas of the implant collar in the control with primary stability. (b) Bone tissue filled the areas on the first coronal thread in the polymer with primary stability (PPS) group. On the implant collar in the PPS group there was contact with fibrous tissue. **Figure 4.** (a) The control without primary stability (C) group showed the bone tissue located at the areas of the implant collar. (b) In the polymer without primary stability (P) group, there was contact between bone and the threads in the medullar area at 40 days. Note the presence of the polylactic acid/polygalactic acid copolymer located in the medullar space. **Figure 5.** At 90 days, in (a) there was discontinuance between the bone tissue and the implant surface on the implant collar (C group). (b) In the P group, the bone filled the implant collar and the first coronal thread areas, and there was major contact between the implant surfaces.
groups and time periods, according to the criteria evaluated (ANB, CFT, and CIC).

**DISCUSSION**

The use of rabbit tibia bone as a model to evaluate the osseointegration of different types of implants has been widely used in the literature. The most used place in this experimental model is the medial-proximal region of the tibia\(^2\) and the tibial metaphysis.\(^2\)

The primary stability of implants is one of the main factors influencing the survival rates of the implant. It is considered a prerequisite for establishing mechanical support, which is essential to the process of osseointegration,\(^2\) as unstable implants result in fibrous encapsulation.\(^2\) In this study the presence of new bone formation was verified around implants installed with and without primary stability and confirmed by qualitative and quantitative analysis. However, in the groups with implants installed without primary stability, the bone formation was lower than in the stable groups after 40 days. The movement of the implant during the bone-healing process leads to a lack of mechanical support and initial delay and consequent reduction in bone formation and establishment of an interface with the implant surface. At 90 days, this difference is not observed because of the secondary stabilization of the implant. Akimoto et al\(^2\) concluded that the width of the bone defect directly influences the percentage of bone-implant contact; however, in their study the implants were installed with primary stability.

Although high success rates have been reported with the use of osseointegrated implants,\(^3\) failures may be observed in bone of poor quality or in situations of reduced bone volume.\(^3\) Moreover, after tooth extraction, the alveolus often presents dimensions larger than the diameter of a conventional implant, forming a gap that affects the acceptable bone-implant contact. Use of the PLA/PGA copolymer favored the primary placement of implants and subsequent bone formation at 40 and 90 days in groups without primary stability. This finding may be explained by the statistical difference between groups P and C in both periods. In the

| TABLE 1. Maximum, mean, minimum, and SD of ANB (%)* |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **ANB** | **CPS Group** | **C Group** | **PPS Group** | **P Group** |
| 40 days | Maximum | 72.89 | 77.94 | 90.33 | 68.44 |
| | Mean | 68.50 | 72.81 | 80.06 | 62.96 |
| | Minimum | 64.34 | 68.36 | 64.66 | 57.50 |
| | SD | 3.23 | 3.74 | 10.69 | 4.14 |
| 90 days | Maximum | 95.78 | 86.58 | 94.76 | 81.76 |
| | Mean | 91.42 | 82.73 | 88.11 | 79.77 |
| | Minimum | 84.39 | 78.25 | 80.43 | 74.17 |
| | SD | 4.30 | 3.50 | 5.98 | 3.24 |

*ANB indicates area of newly formed bone; CPS, control with primary stability; C, control without primary stability; PPS, polymer with primary stability; P, polymer without primary stability.

| TABLE 2. Maximum, mean, minimum, and SD of CFT (%)* |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **CFT** | **CPS Group** | **C Group** | **PPS Group** | **P Group** |
| 40 days | Maximum | 84.74 | 63.14 | 66.67 | 56.94 |
| | Mean | 79.47 | 60.77 | 63.53 | 54.63 |
| | Minimum | 75.82 | 58.17 | 61.67 | 52.03 |
| | SD | 3.62 | 1.82 | 2.13 | 1.99 |
| 90 days | Maximum | 88.57 | 87.89 | 81.08 | 67.98 |
| | Mean | 80.20 | 84.42 | 76.44 | 66.53 |
| | Minimum | 66.03 | 79.56 | 71.28 | 63.54 |
| | SD | 10.09 | 3.43 | 3.50 | 1.77 |

*CFT indicates contact between the bone and implant surface on the first thread; CPS, control with primary stability; C, control without primary stability; PPS, polymer with primary stability; P, polymer without primary stability.
analysis of the CIC of these groups, the presence of the copolymer favored the maintenance of primary placement of implants, serving as a mechanical support and a framework for the process of bone formation\textsuperscript{18} and reducing movement.

In groups of implants with primary stability, a higher bone formation was observed in the CPS group than in the PPS group after 40 days. This result is related to the presence of the copolymer, which undergoes a process of degradation by hydrolysis as it is gradually replaced by newly formed bone tissue, delaying the repair process. However, the polymer was demonstrated to be osteoconductive because of the presence of a large percentage of new bone formation in the PPS and P groups at 90 days (mean 88.11\% and 70.77\%, respectively), as noted by other authors.\textsuperscript{18,22–24}

The association of the PLA/PGA with other biomaterials is also being tested, as reported by Hassan.\textsuperscript{32} This author evaluated the association of this polymer with autogenous bone graft, and the results showed significant reduction of probing pocket depth and gains in attachment level in patients with dehiscence around immediate dental implants, suggesting that this as an excellent biomaterial polymeric bone substitute. Thus, maintenance of the primary position of the implants, as shown in our study and in the study by Hassan\textsuperscript{32} may be essential for the success of techniques that involve immediate dental implants.

Therefore, considering the bone formation observed mainly at 90 days in all groups and periods in this study, and based on the methodology and results, we concluded that the PLA/PGA copolymer showed biocompatibility and allowed new bone formation in contact with the implant. The presence of the copolymer delayed bone formation in the group without primary stability but helped to maintain the primary position in the groups without stability. Moreover, osseointegration occurred in both groups, even in the absence of primary stability of implants.

We suggest the need for new research considering this proposed experimental methodology for evaluating different methods of analysis (such as biomechanics, immunohistochemistry, and the scanning electron microscopy) and different periods and types of implants, with or without application of immediate or late prosthetic loads.

The presence of the copolymer resulted in less bone formation in the group without stability but resulted in more bone formation in the group with stability. On the other hand, the copolymer promoted major linear contact between bone and implant, especially in the group without primary stability, at the implant collar, where it was surrounded by cortical bone.

Thus, the PLA/PGA copolymer has an osteoconductive property and enhances bone healing in situations that involve a lack of bone tissue and in critical bone defects. Moreover, this study contributed additional information about the use of the PLA/PGA copolymer as a bone substitute.

**ACKNOWLEDGMENT**

The authors are grateful to the FAPESP (Fundaç\’\~{a}o de Amparo à Pesquisa do Estado de São Paulo - São Paulo Research Foundation) for financial support.

**ABBREVIATIONS**

ANB: area of newly formed bone tissue

C: control without primary stability

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**TABLE 3.**

Maximum, mean, minimum, and SD of CIC (%)

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<tr>
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<th>C Group</th>
<th>PPS Group</th>
<th>P Group</th>
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*CIC indicates contact between the bone and implant surface on the implant collar; CPS, control with primary stability; C, control without primary stability; PPS, polymer with primary stability; P, polymer without primary stability.*
CFT: contact between the bone and implant surface on the first thread
CIC: contact between the bone and implant surface on the implant collar
CPS: control with primary stability
P: polymer without primary stability
PGA: polyglycolic acid
PLA: polylactic acid
PMMA: polymethylmethacrylate
PPS: polymer with primary stability

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