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Tissue response and biodegradation of polylactic acid bone screw and plate

CHANG-CHIH CHEN*† BEY-RONG GUO‡ HOW TSENG§ YI-HUEI WANG*
HAW-MING HUANG‖ WEN-TA CHIU** SHENG-YANG LEE*,**

* *Graduate Institute of Oral Rehabilitation Sciences, College of Oral Medicine, Taipei Medical University, Taipei, ROC.*
† *Department of Emergency Medicine, Mackay Memorial Hospital, Taipei, ROC.*
‡ *School of Dentistry, College of Oral Medicine, Taipei Medical University, Taipei, ROC.*
§ *Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, ROC.*
‖ *Graduate Institute of Oral Sciences, College of Oral Medicine, Taipei Medical University, Taipei, ROC.*
***Department of Dentistry, Wan-Fang Hospital, Taipei Medical University, Taipei, ROC.*

Because of the physical, chemical, and biological properties of polylactic acid (PLA), it is a potential material for orthopedic surgery. To study the tissue response to and degradation of PLA in bone tissue. The materials used included PLA bone screws and plates which were composed of 5% D-form and 95% L-form polylactide. Custom-made bone screws, bars, and plates were studied, using commercial products as controls. The materials were implanted into 24 New Zealand white rabbits by optimal methods and removed after 1, 4, 8, and 12 weeks for histological and physical examination. The tissue response revealed good biocompatibility. There was no difference in weight loss with an increase in time. The bending load and molecular weight decreased with an increase in time. The initial bending load of the commercial plate was stronger and significantly decreased with an increase in time. The bending load of the custom-made products was more stable than that of the commercial products. It is clear that the bending load decreased as the molecular weight decreased during the degradation process. However, there was no simultaneous weight loss. It is evident that the custom-made plates produced by injection-molded had a lower molecular weight but maintained adequate strength for as long as did the commercial plates. These results suggest that the self-manufactured screws and plates have good bone tissue reaction. The custom-made PLA products had higher strength with a similar molecular weight. They underwent the same degradation process as commercial products. In addition, they can shift the load to the healing bone as time passes. They thus meet the demands of ideal orthopedic devices.

Key words: polylactic acid, bone screw/plate, biocompatibility, biodegradable.

It is very important that bioresorbable materials should meet the following criteria for use in orthopedic surgery: (1) sufficient strength for fixation of bone fractures until complete healing occurs, (2) no side effects and no undetectable intermediate products during the process of degradation, and (3) completely degradable material [1]. Therefore, the ideal bioresorbable osteosynthetic material should possess: (1) good biocompatibility, (2) skeletal-like viscoelasticity, (3) sufficient mechanical properties, and (4) adequate degradation. The material should not be absorbed until the fracture has completely healed, and should gradually lose its strength and conduct stress to the healing bone. It should be unnecessary to remove the material surgically, and there should be no concern about stress-shielding effects which can lead to secondary fracture [2-5]. Absorbable high-molecular-weight materials have been developed as a new technology for osteosynthesis.

Bioresorbable osteosynthetic material can be divided into 3 major kinds: glycolide PGA, the copolymer of poly(glycolide) (PGA) and poly(lactide) (PLA), and pure polylactic acid. When we use PGA or copolymer of PGA/PLA, the lower molecular weight and faster degradation rate of PGA may result in a severe non-specific inflammation reaction which significantly affects the biocompatibility [6]. Pure PLA meets most of the above-mentioned criteria; it has the greatest development potential and has come closest to being the ideal osteosynthetic material [7,8]. The degradation rate of PLLA is slower than those of PGA and PGA/PLA copolymers. For this reason, further studies have focused on PLLA, which can maintain its strength longer [9]. However, there are still some shortcomings that remain unresolved. Elst et al [10] indicated that the strength of cortical bone is 80 to 150 MPa, and the elastic modulus is 0.6-10.3 GPa. According to the literature, the strength of PLLA is around 11.4-145 MPa. It is thus evident that, the strength is generally insufficient for fixation of cortical bones. In addition, its mechanism of degradation in tissues is still unclear [11]. Even though its strength can be increased by enhancing the crystallinity and molecular weight of the macromolecules, higher molecular weight may lead to lower degradability. For these reasons, research has been based on the characteristics of PLA but has taken different directions, including: a self-reinforcing method [12,13] with low-molecular-weight PLLA complex material, or PLLA and PDLA intermixed complexes with variable proportions [14], or PLLA and hydroxyapatite (HA) [1] complex material.

In order to develop and examine osteosynthetic materials which meet the criteria mentioned above, this study adopted injection-molded low-molecular-weight PLA bone screws and plates, co-developed and researched by our lab and BioTech One (BTO) Inc., Taipei, Taiwan, so that results of in vivo tissue reactions and degradation may serve as guidelines for future manufacturing procedures and clinical applications.

MATERIALS AND METHODS

The materials used for the study group included test bars (22 × 6 × 2mm), bone screws (8 mm long, 2 mm in diameter), and bone plates (22 × 6.8 × 1.3 mm; 4-hole, 2.6 mm in diameter) made of high-molecular-weight polymers of polylactide (molecular weight 140 kDa), consisting of poly-5D/95L-lactide, prepared by injection-molding in a clean room (class 5000), with a glass transition temperature (Tg) of 62±2°C, a melting point (Tm) of 150±2°C, and a crystallinity of 37.85%. They were packed and sterilized with γ-ray (15 kGy, Nuclear Institute, Long-Tang City, Taoyuan, Taiwan); the MW was about 102 kDa (after radiation). We used commercial MacroPore

products (MacroPore Biosurgery IRC, San Diego, CA, USA), including screws (5 mm long, 2 mm in diameter) and bone plates (22 × 6.7 × 1.6 mm; 4-hole, 2.0 mm in diameter) as the control group, consisting of poly-15D/85L-lactide (molecular weight 166 kDa), with a glass transition temperature of 65~70℃.

Twenty-four New Zealand white rabbits (3-4 months old, 3-4 kg in weight) served as the experimental model. Before implantation, the rabbits were weighed and given atropine prior to anesthesia; 10~15 minutes later, pentobarbital sodium (1 mg) was injected into the rabbit's ear vein to achieve general anesthesia. In addition, a prophylactic dose of gentamicin was given. After shaving and sterilization, the operation area of implantation, located on the anterior side of the lower leg, was anesthetized with a mixture of 0.25% Marcaine and epinephrine (1: 200,000) by local subcutaneous infiltration for homeostasis and prolonged analgesia.

Rabbits were then divided into 3 groups. Group A (6 rabbits) received a 4~5 cm incision along the anterior side of the tibial bone with a scalpel; this was continued down layer by layer until the bone was exposed. Three holes were drilled in the right side of the tibia using a thread diameter of 1.65 mm with copious saline irrigation to prevent heat damage. One BTO screw and 1 MacroPore screw were then placed 1 cm apart. No screw was placed in the third hole, which served as a control. Meanwhile, 2 holes were also drilled in the left tibia, and 2 BTO screws were inserted. As a control, no hole was drilled nor screw placed in the location corresponding to the third hole in the right tibia (Figure 1). Group B (12 rabbits) had test bars implanted according to the onlay model[15]. A 3~4 cm incision along the anterior side of the tibia was made which was continued down layer by layer until the bone was exposed. The test bar was attached onto the surface of the bone (Figure 1). Group C (6 rabbits) also had a bone plate implanted according to the onlay model. A 3~4 cm incision was made along the anterior side of the tibia which was continued down until the bone was exposed. A self-made bone plate was attached onto the surface of the left tibia, and a commercial bone plate was attached onto the right one (Figure 1). After implantations, periosteum membranes and muscles were repaired with Dexon sutures and the skin with nylon ones. Then, all study rabbits were moved to a recovery room and revitalized with a warmth-maintenance system prior to sending them back to their respective cages. All rabbits were fed a regular diet and given gentamicin intramuscularly for 5 days postoperatively to prevent infection.

Specimens from groups A and C were harvested at 1, 4, and 12 weeks postoperatively. Specimens from group A were then fixed with 10% formaldehyde (50~70 ml) for 5 days, followed by decalcification. The screw was removed and the hole was exposed. Decalcified tissue blockembedded in the hole was transected into 3 smaller blocks. These smaller tissue blocks were dehydrated in 80%, 90%, 95%, and 100% alcohol for 1 hour each. Dehydrated tissues were kept in 100% alcohol for another hour and then in xylene for an additional hour. One hour after infiltration with paraffin, tissue blocks were dissected into sections 5 μm in thickness. Sections were dried overnight in an oven. The paraffin was then removed by xylene, which was in turn removed by immersion in 100%, 95%, and 80% alcohol for 2 minutes each. Subsequently, sections were rinsed with running water for 10 minutes, and then immersed in Harris hematoxylin solution for 2 minutes. Then sections were rinsed again with running water for 1 minute and immersed in ammonia for 1 minute. Sections were next washed with running water for 10 minutes, and immersed in eosin solution for 5 minutes. Sections

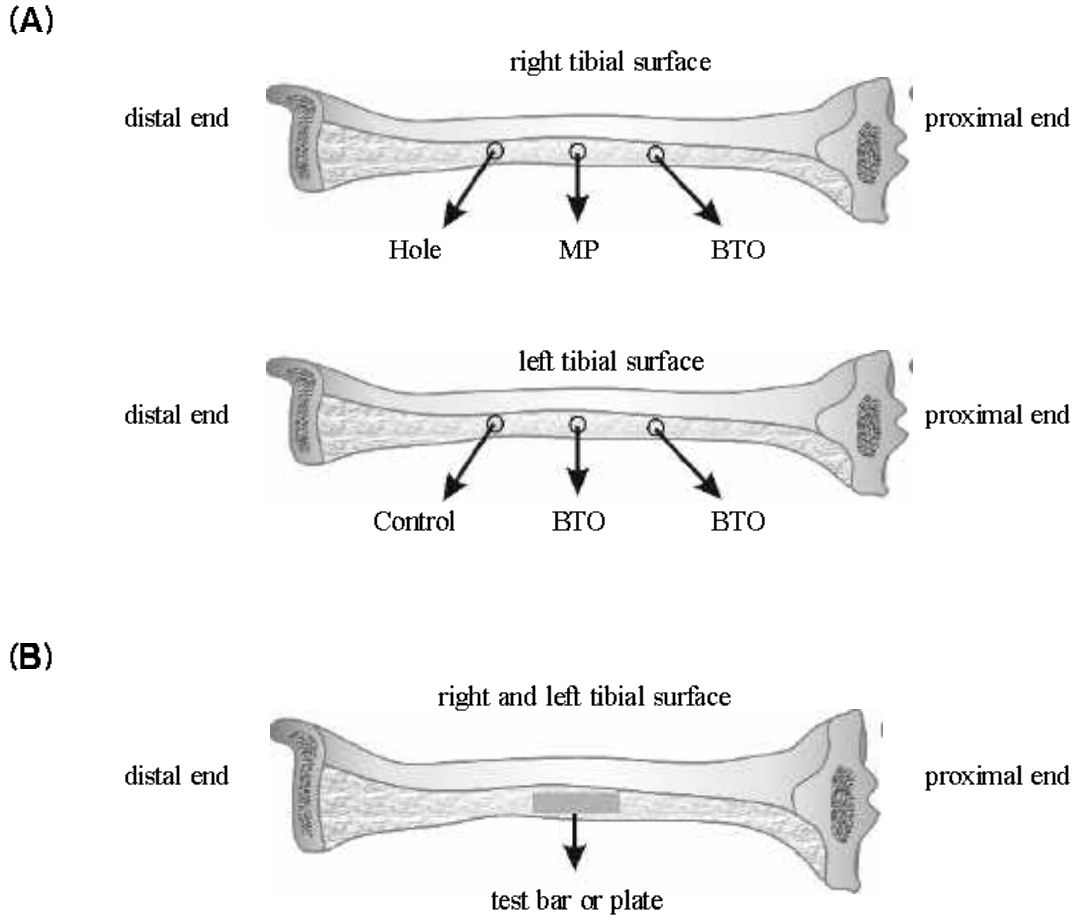
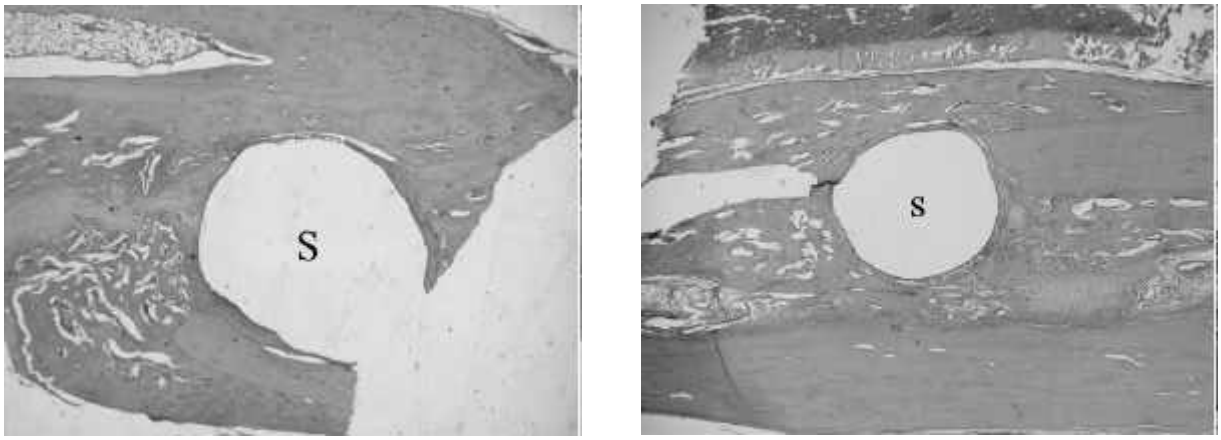


Figure 1. *Diagrammatic representation of the tibia showing.*
(A) Group A implantation methods: BTO, self-manufactured bone screw; MP, commercial bone screw; Hole, no screw implantation; Control, no hole and no screw.
(B) Groups B and C implantation methods: 1 test bar on the surface of each tibia by the onlay model (B group), 1 BTO plate on the surface of the left tibia, 1 MP plate on the surface of the right tibia by the onlay mode (C group).

were placed in 70%, 80%, 90%, 95%, and 100% alcohol for 1 minute each and were then placed in a mixture of 100% alcohol and xylene (1:1) for 2 minutes and immersed in xylene for 2 minutes twice. The slide was covered with an Entellan coverslip, and the tissue reactions were examined under a light microscope.

Specimens from group B were harvested at 1, 4, 8, and 12 weeks postoperatively. In vivo biodegradation analysis was performed in group B and C specimens. Specimens were placed in an incubator set to a temperature of 37±2°C. After the weight had stabilized to within 1%, the weight loss was measured using an electronic calibrator (Mettler-Toledo, AG245, CH-8608 Greifensee Switzerland). Changes in mecha-



(BTO) (MP)

Figure 2. *The histological results of Group A, 4 weeks.*
The appearance of the interface between the screw(S) and the cortical bone showed a fibrous capsule with new bone growth in both BTO and MP groups. (40x) (H&E stain)

nical strength were measured with a Material Testing System (MTS, MTS corp., 858 Mini Bionix, Eden Prairie, MN, USA). Changes in molecular weight were determined by gel permeation chromatography (GPC, Series 200: detector, pump, column, PerkinElmer, 761 Main Avenue, Norwalk, CT, USA). Morphological examinations were carried out using scanning electronic microscopy (SEM, S-2400, Hitachi, Tokyo, Japan), exclusive of group C. The degree of crystallization was measured using differential scanning calorimetry (DSC: PerkinElmer, 761 Main Avenue, Norwalk, CT, USA), exclusive of group C. The t-test was used for statistical analysis, and $p<0.05$ was considered statistically significant.

RESULTS

In group A, acute inflammation was noted 1 week after implantation in both the study and control groups. Loose fibrous capsules with ill-defined borders and cell infiltration dominated by neutrophils and lymphocytes were also found. A few macrophages were noted in the study group. After 4 weeks (Figure 2), the fibrous capsules were still loose, and many fibrocytes were found in the study group. Fewer inflammatory cells but more lymphocytes were found than after 1 week. In week 12, there was even less of an inflammatory reaction in the BTO group; however, more inflammatory cells and hemorrhaging were found in the MP group. In both groups, fibrous capsule formation was seen, but no macrophages were found. In the control group, complete healing of the bone tissue but no fibrosis was seen.

In the onlay group (group B), the test bar was covered by bone tissue by week 12. By 1 week after the operation, the morphology of the test bar had not changed, but the transparency was slightly reduced. By week 4, the transparency of the implant was unevenly reduced, but still no variation in morphology was found. By week 8, the test bar appeared heteroge-

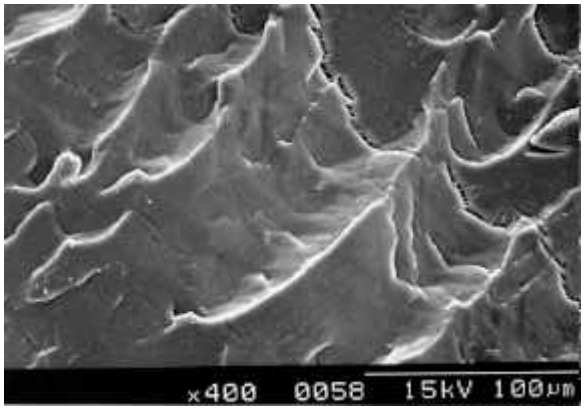


Figure 3. *SEM-figure of a test bar after implantation. The rugged protuberances on the broken surface were more distinct with time.*

neously milky white, the surface remained smooth, and the transparency had decreased. By week 12, the implant remained intact but indented absorption spots were noted on the surface. SEM showed pores at the break surface by week 4, and by week 8, the pores increased in number and size, the rough protrusions on the surface were more marked, and breaking channels were straighter and wider (Figure 3).

The strength of the test bar (Figure 4) was 149 ± 7 MPa initially and had decreased to 145 ± 9 MPa by week 1, 135 ± 10 MPa by week 4, 110 ± 9 MPa by week 8, and 85 ± 2 MPa by week 12. The strength decreased by 3% to 43% ($p<0.01$), and markedly varied with time. Figure 4 shows that the strength of the custom-made bone plate (BTO) was 35 kgm initially and

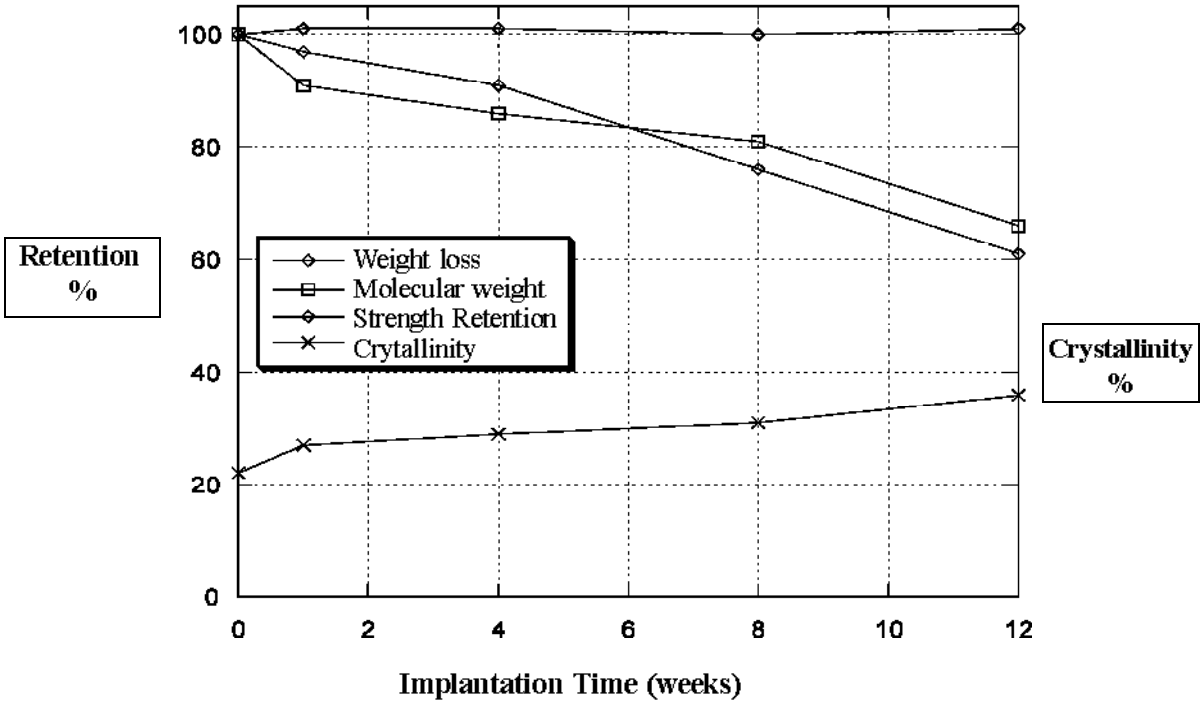


Figure 4. *Group B: retention of weight loss, molecular weight, bending load, and crystallinity of the test bar for various implantation times.*

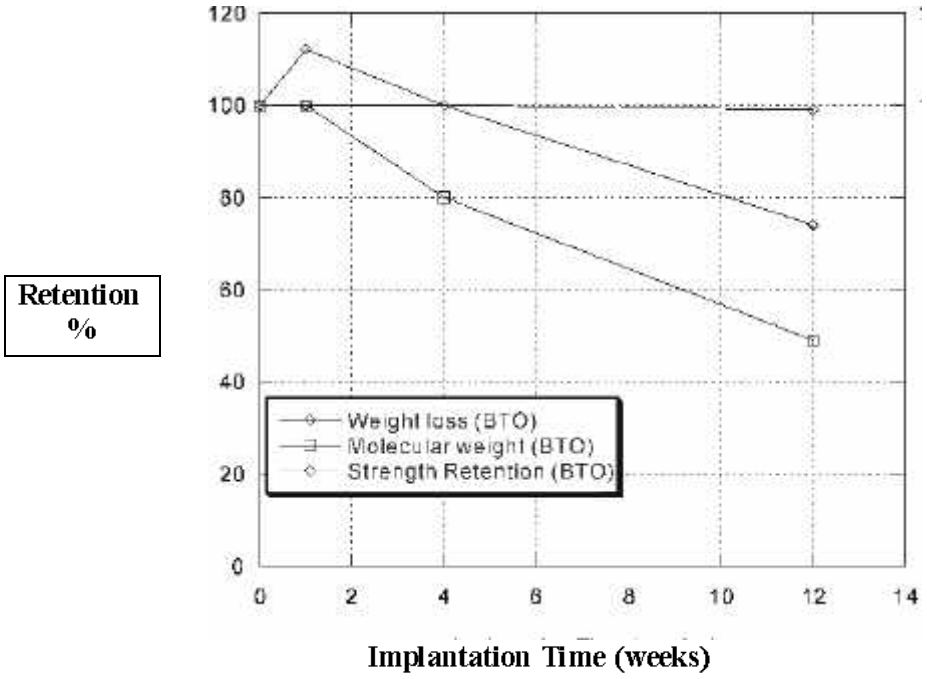


Figure 5. *Group C: retention of weight loss, molecular weight, and bending load of the BTO plate for various implantation times.*

through week 4. It had decreased to 26 kgm by week 12 (a 26% decrease, $p<0.05$). The strength of the commercial bone plates (MP) was 50 kgm initially and had decreased to 39 kgm by week 4 (a 42% decrease, $p<0.05$). The result showed that the strength of the MP bone plate decreased faster than did the BTO bone plate from weeks 1 to 4 ($p<0.05$).

In group B, the molecular weight of the test bar was 102 kDa before implantation. It was reduced to 93, 88, 83, and 67 kDa by weeks 1, 4, 8, and 12, respectively (Figure 4). The reduction was 3%~34% ($p<0.01$). In group C, the molecular weight of the custom-made bone plate was 103 kDa before implantation. At weeks 1, 4, and 12, it was 103, 82, and 50 kDa, respectively (20%~50% reductions, $p<0.01$) (Figure 5), while the molecular weight of the commercial bone plate was 166, 118, and 117 kDa, respectively (29%~57% reductions, $p<0.01$) (Figure 6).

The degree of crystallization of the test bar was 22% in group B before implantation, and it had increased to 27%, 29%, 31%, and 36% by weeks 1, 4, 8, and 12, respectively (Figure 4). The test of crystallization was not performed in group C because the commercial bone plate is amorphous.

During the 12 weeks of in vivo biodegradation, the molecular weights of both custom-made test bar and bone plate decreased first, the bending strength decreased along with molecular weight, but weight loss did not occur (Figures 4, 5). The degree of crystallization in-

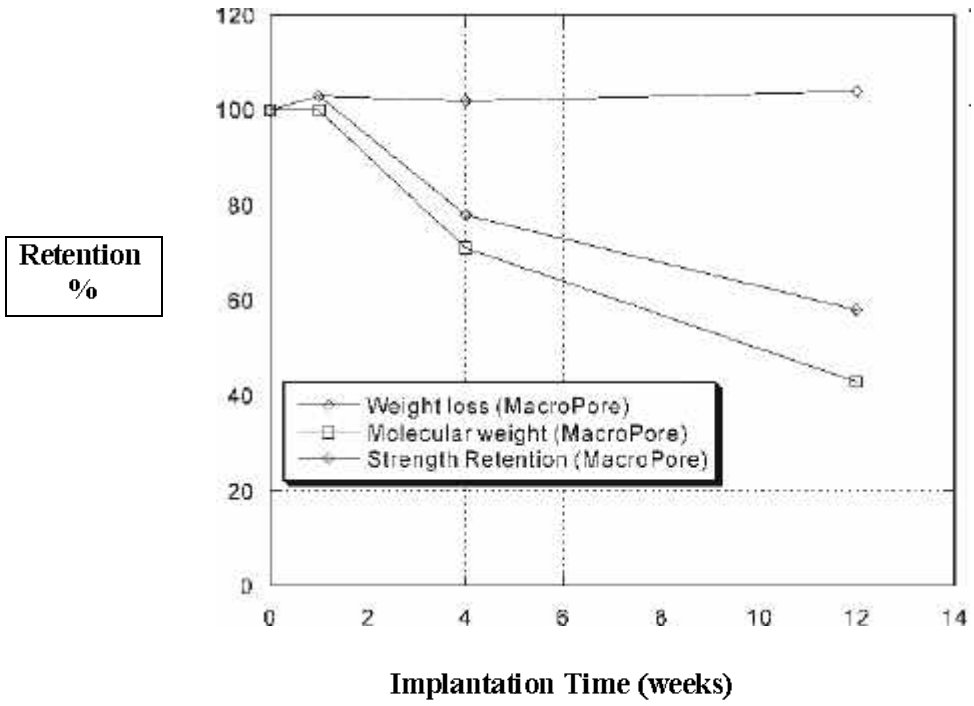


Figure 6. *Group C: retention of weight loss, molecular weight, and bending load of the MP plate for various implantation times.*

creased with the time of implantation. Comparing Figures 5 and 6, the biodegradation tendencies of the custom-made bone plate and commercial bone plate were similar. The weight and strength of the custom-made bone plate and commercial plate increased initially in week 1, and then the strength gradually declined with time. With a lower molecular weight, the thinner custom-made bone plate degraded in a slower manner initially, and its strength was sustained for a longer period. This difference only became insignificant by week 12.

DISCUSSION

Animal implantation models are important in vivo experimental models used to evaluate tissue toxicity of medical devices. Polylactide is considered a non-toxic and non-antigenic medical material of high molecular weight. This study compared polylactide products with commercially available products by implanting both screws and plates into rabbit tibias for 12 weeks. All animals survived and grew well without general or localized complications. Histological examination showed that the tissue response to our polylactide was similar to that of generally biocompatible materials.

In vivo biodegradation of PLA
Weight loss and crystallization

The 12-week observation of in vivo degradation of the test bar showed that the bar

weighed 0.3775 g before implantation and increased to 0.3813 g by week 12. The weight increased by 0.0038 g (101%). This slight increase may have been due to absorption of water from the surrounding tissue. The molecular weight was 102 kDa before implantation and decreased to 67 kDa by week 12, which was 66% of the original weight. In addition, the bending strength of the test bar was 149 MPa before implantation and had decreased to 89 MPa by week 12, which was 58% of the original weight. Only the degree of crystallization had increased from 22% before implantation to 36% by week 12. The molecular weight-related decrease in bending strength may have been caused by the hydrolysis-induced breakdown of ester linkages. The custom-made bone plate is 1.3 mm in thickness, thinner than the commercial MacroPore bone plate (1.6 mm). Thickness is one of the factors affecting the course of biodegradation. Biodegradation during initial hydrolysis in thicker polylactide materials starts at the amorphous part. A decrease in inertia of the molecular chain led to increased molecular mobility and breakdown, and recrystallization subsequently developed. This may explain the increase in the degree of crystallization in this study. This increase in crystallization compensated for the shortage of mechanical strength resulting from a reduction in molecular weight; therefore, the bending strength of the custom-made BTO plate did not decrease too rapidly. The commercial product, MacroPore, did not elicit such a phenomenon because it is amorphous in structure; therefore, its bending strength dramatically decreased when the molecular weight decreased.

In the initial phase, the molecular weight of the test bar significantly decreased; it then reached a steady state during the late phase. This phenomenon suggests that hydrolysis-induced breakage of ester linkages is a crucial mechanism of biodegradation. Each ester linkage is subject to hydrolysis. During the initial phase, the molecular chain of P(L/DL)LA is longer, and many more sites are available for hydrolysis resulting in a faster reduction in molecular weight. If only the action of hydrolysis contributed to biodegradation, the rate of the molecular weight decrease would supposedly slow down with time; however, biodegradation of the molecular weight appeared to accelerate between weeks 4~8 and slow down after week 8. The above condition suggests that the degradation materials might self-catalyze. In the early phase after P(L/DL)LA implantation, the dramatic reduction in molecular weight with a relatively insignificant loss of weight was mainly due to absorption of surrounding water molecules. After degradation into smaller and medium-soluble molecules, the weight loss became evident.

Mechanical strength and crystallinity

Mechanical strength is an important index for bio-absorbable osteosynthetic materials. This study showed that injection-molded custom-made polylactide has good mechanical strength (149±7 MPa). Even though PDDLA with 5% amorphous components resulted in a reduction in the overall degree of crystallization, it elicited high strength under a low molecular weight, which resembles the mechanical properties of human bone. The loss in mechanical strength with degradation of molecular weight occurred simultaneously. During substantial polylactide degradation, the mechanical strength is lost faster. PDLLA, being the amorphous part, is degraded first. Therefore, if PDLLA makes up too large of a proportion, degradation is too fast, the mechanical strength dramatically decreases, and there is no self-catalysis.

The finding of bigger pores in week 8 compared with week 4 suggests that the ma-

terials underwent local liquefaction[16], resulting in more-prominent rugged protuberances with time. Increases in flexibility and tensile strength of the test bar are probably due to an increase in the degree of crystallization. A rabbit's body temperature is about 38~39.5℃, at rabbit's which the inserted plate elicits smaller crystallization grains, greater strength, and straighter and wider break surfaces.

Degradation starting after bone healing is an ideal characteristic of osteosynthetic materials. In our study, the strength of group B had decreased to 135 MPa by week 4. Since the human metabolic rate is 3 times a rabbit's metabolic rate[17,18], 4-week-old rabbits are comparable to 12-week-old humans. It takes 6~8 and 8~12 weeks for healing of human mandibles and femurs, respectively. Therefore the mechanical strength should be sufficient for human bone.

Histological reaction

In the initial phase of implantation with the commercial plate (MP), degradation was faster due to easier water penetration into the porous amorphous structure. Recrystallization occurred with time and irritated adjacent tissues because of an increase in hardness. Irritation caused by the MacroPore bone plate was more severe than that from the custom-made bone plate because the MacroPore bone plate is amorphous and rapidly degraded. Furthermore, by week 12, inflammation caused by the MacroPore plates was more significant than that caused by the custom-made bone plates. It is therefore inferred that lactic acid released during degradation further triggers the inflammatory reaction by reducing pH values of surrounding tissue. Previous reports[6,10] and our study have demonstrated that PLA induces aggregation of fibroblasts, and its osteoconduction is not significant. Hydroxyapatite has osteoconduction properties[1], so it can be included in future product developments.

Transcortical implantation research has been prioritized by many researchers[19-22]. The thickness of capsule formation after implantation reflects internal biochemical and external mechanical activities. It is improper to regard the thickness of the capsule as an indirect measure of the cellular reaction because mechanical irritation caused by movement and attrition of the screw and plate may also thicken capsules. The onlay model was used in our study to implant custom-made test bars; significant hyperemia, inflammation, and new growth of bone tissue beneath the bar were found during the histological examination. This may have been caused by attrition between the test bar and bone. According to specifications in the literatures[23,24], high cell activity is the major tissue reaction occurring 1 week after implantation, and after a transitional state, it reaches a steady state after 9~12 weeks. In our study, group A demonstrated tissue reactions matching those of previous reports.

CONCLUSIONS

Injection-molded custom-made polylactide bone plates and screws provided better strength than commercial products with similar molecular weights and elicited well-tolerated reactions with bone tissue at 12 weeks. The gradual decrease in mechanical strength was consistent with that of commercial products. With the ability to shift stress to healing bones, our bone plate is a device with great potential for internal fixation during oral maxillofacial surgery.

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聚乳酸系骨釘骨板之組織反應與降解變化

陳長志*† 郭倍榮‡ 曾 厚§ 王益暉* 黃豪銘‖ 邱文達** 李勝揚*,**

* 台北醫學大學口腔醫學院口腔復健醫學研究所
† 馬偕紀念醫院急診醫學科
‡ 台北醫學大學口腔醫學院牙醫學系
§ 台北醫學大學醫學院醫學研究所
‖ 台北醫學大學口腔醫學院口腔科學研究所
** 台北醫學大學附設萬芳醫院牙科

生物可吸收性材料於骨折手術時需考量的是：良好的生物相容性、近似骨頭的黏彈性、足夠的機械性質，及合宜降解性，不會在骨癒合前即開始吸收，會隨著時間失去強度使應力能逐漸傳導到癒合中的骨頭，既不必第二次手術取出，亦無應力遮蔽效應所產生二次骨折之虞，均符合聚乳酸系高分子之性質，使得可吸收性聚乳酸系高分子之研發逐漸成為製造骨接合材料之新技術。目的在觀察自製射出成型聚乳酸系骨釘骨板在骨組織內的組織反應與降解變化，做為製程改善與未來臨床使用之參考。所用材料成份含 5%右型及 95%左型的聚乳酸共聚合物製成之骨釘、長型片及骨板做為實驗組，另取市售骨釘及骨板做為比較用。以紐西蘭兔為實驗動物，並將所使用材料分別以適當方式植入動物體內後，各於時間點將植入物取出，進行各種測試，包括組織切片觀察，三點彎曲變化、質量損失、分子量變化、結晶度變化與掃描式電子顯微鏡觀察。在組織切片中，初期的實驗組及對照組出現急性炎症反應，繼而轉為慢性炎症反應，到幾乎全消失。在物理性質方面，12 週內的質量損失均不明顯，而初始彎曲負荷隨時間增加而下降；重量平均分子量也隨時間增加而下降。強度方面，市售骨板因較厚，其起始強度(bending load)較強（50 kgm），但隨時間增加而下降；而自製骨板起始強度只有 35 kgm，隨時間增加而下降並不明顯。此結果顯示，吸收性高分子聚乳酸在動物體內的降解過程中分子量會先下降，而整體彎曲負荷也隨著下降，但質量並沒有明顯減輕，且自製骨板雖分子量較低且較薄，然而強度卻維持較久。射出成型自製的聚乳酸性骨釘骨板可能比近似分子量之商品強度高，於 12 週內具有良好之骨組織反應，且於降解過程中機械強度呈漸減，顯示可將承受應力傳導至癒合中骨頭，符合理想之骨接合材所需。

關鍵詞：聚乳酸，骨釘／骨板，生物相容，生物降解。

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Reprint requests to: Dr. Sheng-Yang Lee, Graduate Institute of Oral Rehabilitation Sciences, College of Oral Medicine, Taipei Medical University, No. 250, Wu-Hsing Street, Taipei, Taiwan 110, ROC.