Comparison of Tissue Reaction and Osteointegration of Metal Implants between Hydroxyapatite/Ti alloy Coat : An Animal Experimental Study

PIBUL ITIRAVIVONG, MD*,
THADA LAIPRASERT, MD*,
SOMSAK KUPTNIRATSAIKUL, MD*,
ROBERT B HEIMANN, PhD****
ATICHAT PROMASA, DVM**,
TAWEECHAI TECHAPONGWORACHAI, MD*,
VORANUCH THANAKIT, MD***,

Abstract

Background : One important clinical application of hydroxyapatite (HA) is coating on metal implants to stimulate osteo-integration thus enhancing fixation of the implant to bone, especially plasma-sprayed HA coating applied on Ti alloy substrate. The poor bonding strength between HA and Ti alloy has been of great concern to orthopedists. The biocomptable coat such as Ti alloy (TiO2) coat is one method to improve adhesive strength.

Objective : The objective of this study was to detect and analyze possible differences in bone formation, bone integration and tissue reaction between group I (uncoated Titanium), group II (Hydroxyapatite coated Titanium), and group III (Hydroxyapatite/TiO2 coated Titanium) implant specimens when embedded into bony hosts.

Method : Rectangular specimens were implanted into the femoral bone of adult dogs in randomly different sites including : proximal left, proximal right, distal left, distal right. The tailor-made implant specimens were inserted in 5 x 5 mm preprepared sockets. Radiographic evaluation was taken at 0, 1, 3 and 6 months. All animals were sacrificed at 3 and 6 months post implantation. The femoral bone containing implants were dissected and then prepared to be further investigated. The bone-implant interface was analyzed by H&E surface staining, radiography and scanning electron microscopy. Data concerning percentage of osteointegration and adhesiveness of hydroxyapatite layer from different kinds of implants along the entire length of each implants were collected and analyzed for evaluation of any significant differences.

Results : No osteo-integration was noted in Group I, but there was 25.57 per cent osteo-integration in Group II and 28.63 per cent in Group III. No statistically significant differences were observed between Group II and Group III. However, the coating layer in Group II was found to have detached, in some area, from the metal substrate. Histologically, no adverse tissue reaction was found around any kind of implant.

Conclusion : Biocompatable bond coat is one of the methods to improve adhesive strength of hydroxyapatite coated implants. In the present study it could be concluded that, besides the improvement in adhesiveness, the intervening TiO2 coating layer had no negative effect concerning bone formation and integration and also showed no adverse surrounding soft tissue reaction.

Key word : Titanium, Titanium/Hydroxyapatite Coat, Titanium/Ti Alloy/Hydroxyapatite Coat

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* Department of Orthopedics, Faculty of Medicine,
** Department of Surgery, Faculty of Veterinary Science,
*** Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
**** Department of Mineralogy, Freiburg University of Mining and Technology, D 09596 Freiburg, Germany.

At present, the number of patients receiving biomedical implants to improve orthopedic diseased conditions, such as hip, knee prostheses, is constantly increasing worldwide. The bonding of interface between implant and host tissue is a frequently important problem in clinical use. The bonding can manifest itself in two ways. The formation of a non-adherent fibrous capsule in contact with bioinert or biotolerant materials causes local stress due to movement of the implant(1). A gap can develop between implant and bone which acellular connective tissue can invade. The other way is the mismatch in Young's moduli of bone and the implant material resulting in stress shielding of the bone which could cause bone resorption at a later date(1).

Previously reported studies definitely show that bioactive material, hydroxyapatite, can stimulate new bone formation and promote incorporation of implant into living bone tissue, thus, improving the osteointegration between bone and implant by coating at surface of the implant.

At present, the method of applying hydroxyapatite coating is thermal spray technology(1-6), mostly, astmospheric plasma spray. This technology can provide an bioactive coating of the metal substrate with controlled porosity and sufficient resorption resistance. Chemical purity, phase composition, crystallinity, fracture toughness, cohesive and adhesive strength could be carefully optimized(1).

One of the most important clinical problems of hydroxyapatite coating on metal substrate is the poor bonding strength between hydroxyapatite and implant. Hydroxyapatite melts incongruently because high temperature maintains its presence in the plasma jet and inevitably leads to its thermal decomposition into other calcium phosphates e.g. thermal calcium phosphates (TCP), tetra calcium phosphates (TetraCP) or non biocompatible calcium (CaO). *In vivo*, stability of coating is strongly affected by those decomposition products (Klein 1994)(5).

Microstructure and inhomogenous feature of plasma sprayed hydroxyapatite coat on Titanium study by Wen, Leng(7,8) in the year 2000 showed crystalline and amorphous area in coating lager. Lack of O and OH ions implied the existence of phase other than hydroxyapatite and resulted in excessive adsorption of the coating adjacent to the interface in hydroxyapatite- coated Ti implant(7).

Composition and microstructural change of plasma sprayed hydroxyapatite coating on Ti6Ai4V during incubation in protein free simulated body fluid, dissolution of thermal decomposition products and amorphous calcium phosphate were detected for up to 12 weeks(9).

In the attempt to improve the coating performance, solidly-required in terms of the adhesion of coating substance to the metal substrate and in terms of the biological stability of coating surface in con-

tact with surrounding corrosive body fluid, it can be achieved in several ways. 1) Control of intrinsic plasma spray parameters with the aim to minimize thermal decomposition of hydroxyapatite powder in hot plasm jet. 2) Microstructural engineering of as received hydroxyapatite by short-term annealing at 1,300'c leads to substantial reduction of microporosity (Heimann and Vu 1997)[10]. 3) Application of biocompatible bond coats, whose interfacial interactions with the hydroxyapatite coat and Ti alloy substrate, provides substantially increased adhesive strength as well as acting as thermal barrier coatings to enhance the crystallinity of deposited bioceramic coating system[6,11]. A previous study showed advantage of biocompatible bond coats in improving adhesive strength but most studies experimented *in vivo*, not clinically experimented in real bone tissue. It hasn't been shown how biocompatible bond coat has any effect on bone intregation and tissue reaction. Does biocompatible bond coat improve adhesive strength in animal studies?

The aim of the study was to compare histological and histomorphometric analysis of bone integration and interface reaction around hydroxyapatite coating implants compared with and without biocompatible coating : uncoated Ti6Al14V, HA-coated Ti6Al14V and HA/titaniacoated Ti6Al14V.

MATERIAL AND METHOD

Five healthy dogs, 1.6 to 2.6 years of age (mean 2.2 yrs) were employed for the study. All dogs were radiographed to confirm that their bones were normal.

Anesthesia and Preparation

Pre anesthetic medication was introduced by injecting intramuscularly 0.04 mg/kg atropine sulfate and 0.05 mg/kg acetyl promazine at the thigh area fifteen minutes before sending the dogs to the operating room. Anesthesia was induced by intravenous administration of 2.5 per cent thiopentone sodium (20 mg/kg) and followed by insertion of endotracheal tube. The anesthesia was further maintained by 0.5 per cent - 4 per cent halothane and nitrous oxide with the ratio of oxygen to nitrous oxide one to one.

Operative procedure

After the induction of anesthesia the hair of both lower extremities was shaved. The dog was placed initially in the right lateral position on the operating table and the whole left extremity was disinfected with betadine solution. The dog was also placed in a left lateral position for subsequent operation on the right thigh bone. A longitudinal incision was made on the lateral side from the upper part of the left thigh to the lateral condylar area. The incision was deepened through the subcutaneous tissue and fascia lata to visualize the lateral intermuscular septum and then divided to expose the lateral fermoral condyle and greater trochanter. Bone socket in lateral femoral condyle and greater trochanter were created using a hand drill with the diameter matching the size of implant specimen. Implant specimens were placed in bone socket randomly and tightly fitted. The same procedure was performed on the lateral side of the right thigh in the same dog. The wound was closed with interrupted vicryl sutures for the fascia and the

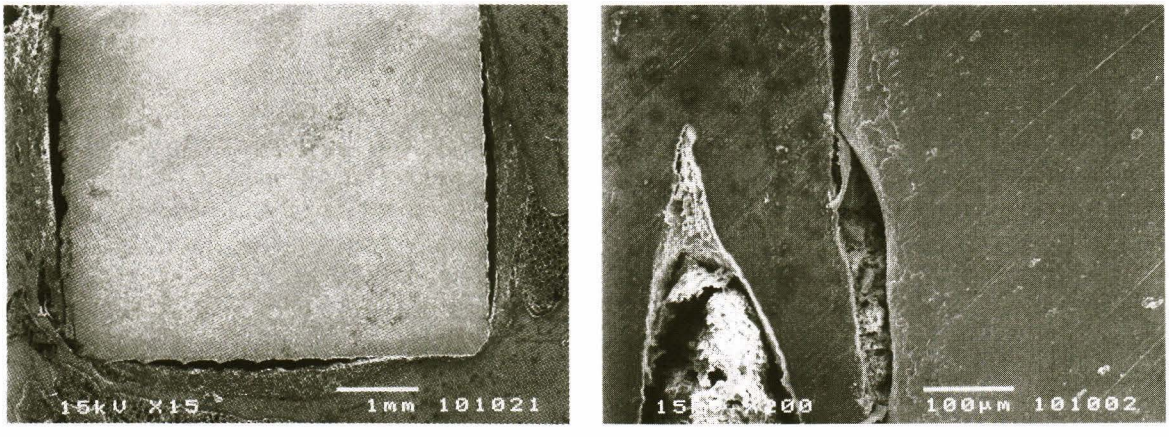

Fig. 1. Specimens of group I (uncoated Titanium) at 6 months.

skin was sutured with black silk. Wound dressing was applied firmly.

Implant materials

All implant specimens were divided equally in 3 groups. Group I was Titanium alloy. Group II was hydroxyapatite coated Titanium alloy. Group III was hydroxyapatite/TiO2 coated Titanium alloy. Each implant specimen was retangular in shape, measuring 5 x 5 mm. A total of 20 implant specimens were surgically embedded in the experimental dogs.

Roentgenographic study

Radiography of the operative implanted area was taken immediately after operation and 1, 3, and 6 months respectively to evaluate any radiographic bonding between bone and implant interface.

Histologic and electronmicroscopic appearance

The dogs were sacrified at 3 and 6 months after material implantation. The femoral bone that contained the implant specimen was dissected and fixed for 7 days in 10 per cent phosphated buffers formalin. Each specimen was cut by slow speed diamond blade machine to preserve the area intended to evaluate the bone bonding interface. Specimens were grounded into thicknesses of 50 micrometer and used for light microscopic examination to evaluate biocompatibility. The remaining samples were prepared for scanning by electron microscope to evaluate bone-implant interface. Electronmicroscopic appearance along the interface of the implant was evaluated for osteointegration and adhesiveness of hydroxyapatite layer. Percentage of osteointegration and adhesiveness of hydroxyapatite layer were measured with an electronic digital caliper by two independent observers.

Statistical analysis

Three types of statistical analysis were uterized in the present study. For comparison of osteointegration percentage between each group, Kruskal Willis test[12] was used. Concerning adhesiveness of hydroxyapatite layer, Mann-Whiney test[12] was employed. Interclass correlation was used to evaluate difference among interobserver measurements.

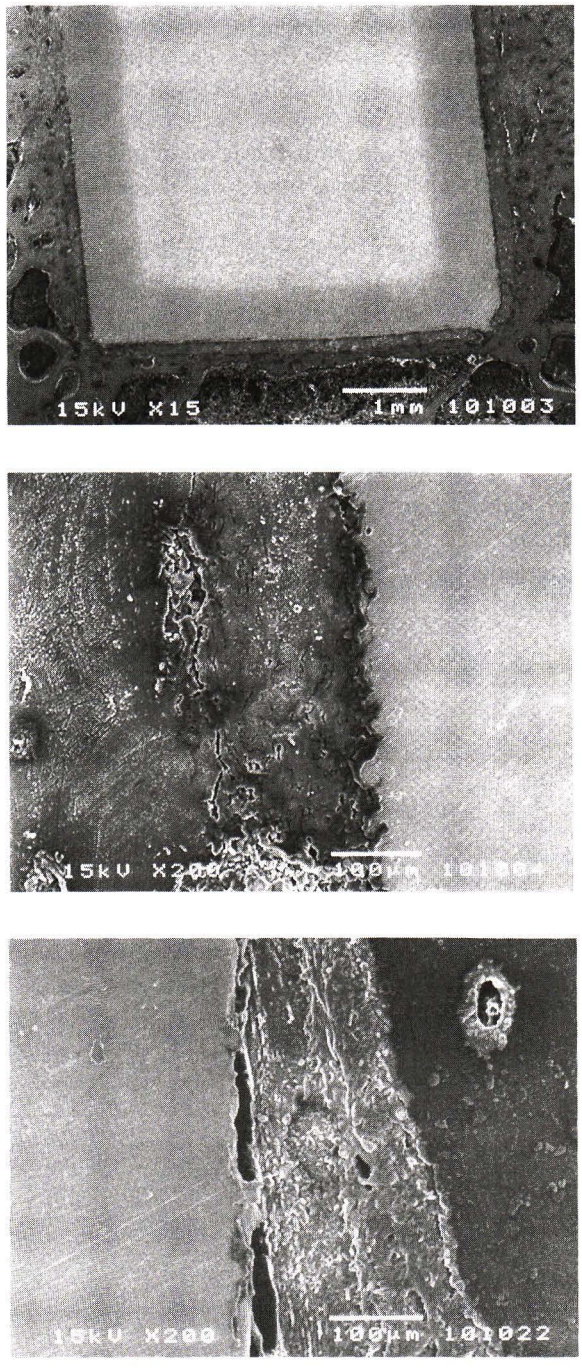

Fig. 2. Specimens of group II (hydroxyapatite coated Titanium) at 6 months.

RESULTS

All dogs were in good health during the experimental period. None of them had wound complications or any tissue reaction during the early or late post-operative period. The dogs could walk normally 2 weeks after surgery.

Soft tissue around the implants was evaluated microscopically by H&E stain at 3 and 6 months after operation. Histologically all groups of implants had shown no tissue rejection. Tissue section in group I had some connective tissue layer in bone-implant interface which differed from group II and III microscopically.

Radiographic appearance of all implant specimens was similar. Radiographic bonding at the bone-implant interface began to be observed 1 month after surgery and complete radiographic bonding was seen 2 months after surgery. No difference was detected among all implant specimens concerning radiographic bone-implant interface.

Scanning electronmicroscopic appearance of the bone-implant interface was evaluated at 3 and 6 months after surgery. At 3 months, group I specimens showed no osteointegration at the bone-implant interface (Fig. 1). In group II and III, some degree of osteointegration at the bone-implant interface was detected (Fig. 2, 3) but there was no significant difference. The mean integration percentage along the cross section surface of the specimens was 25.57 per cent and 28.63 per cent, respectively ($p = 0.458$).

No difference between group II and III concerning adhesiveness of hydroxyapatite layer (92.89% *vs* 95.14% : $p < 0.05$) at 3 months (Fig. 4, Table 1).

At 6 months, in group I, there was a gap between bone and implant and no bonding at the bone-implant interface. (Fig. 3). In group II and III, more bone-implant bonding was observed (Fig. 2-4). Mean integration percentage along the cross section surface of the specimens in group II and III was 80.62 per cent and 82.18 per cent respectively ($p = 0.117$) (Fig. 5, Table 2). As for the results of adhesiveness of hydroxyapatite layer on titanium interface, there were

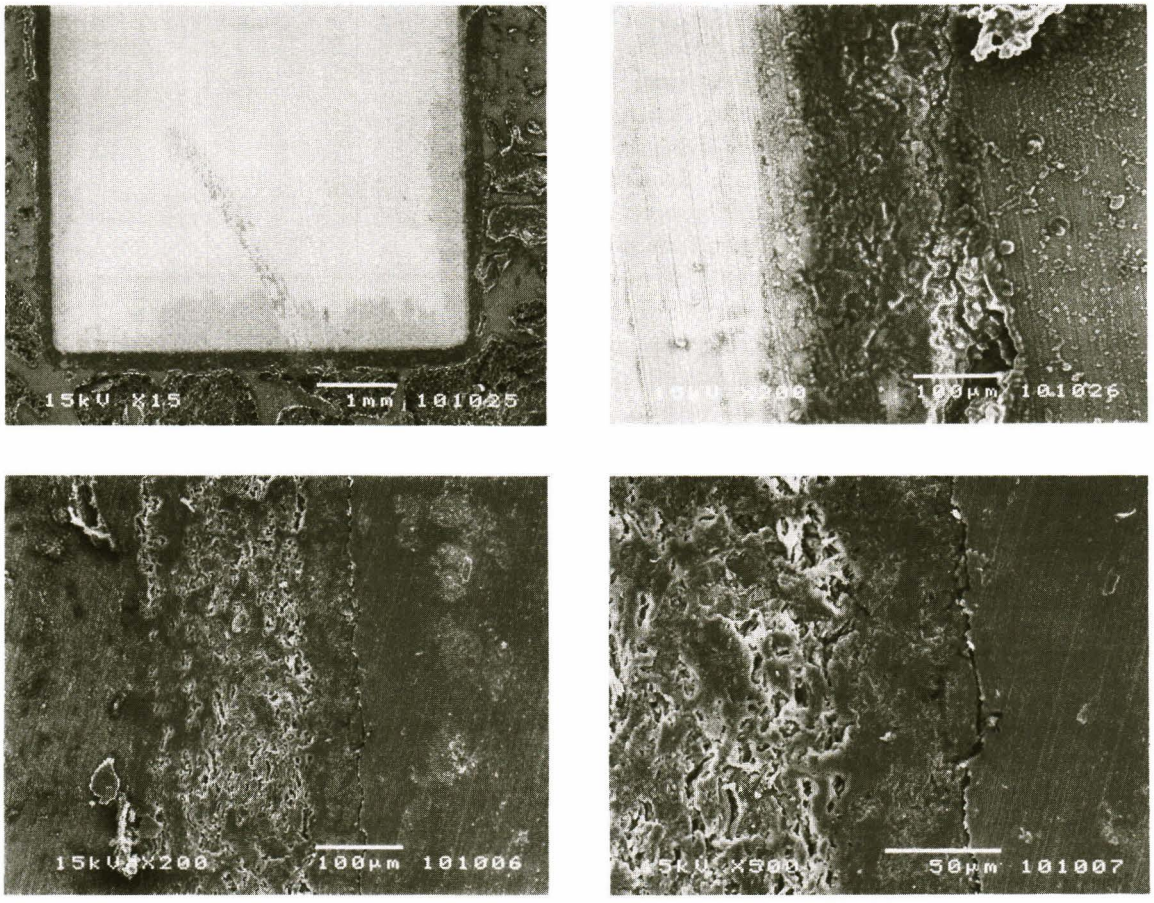

Fig. 3. Specimens of group III (hydroxyapatite/TiO2 coated Titanium).

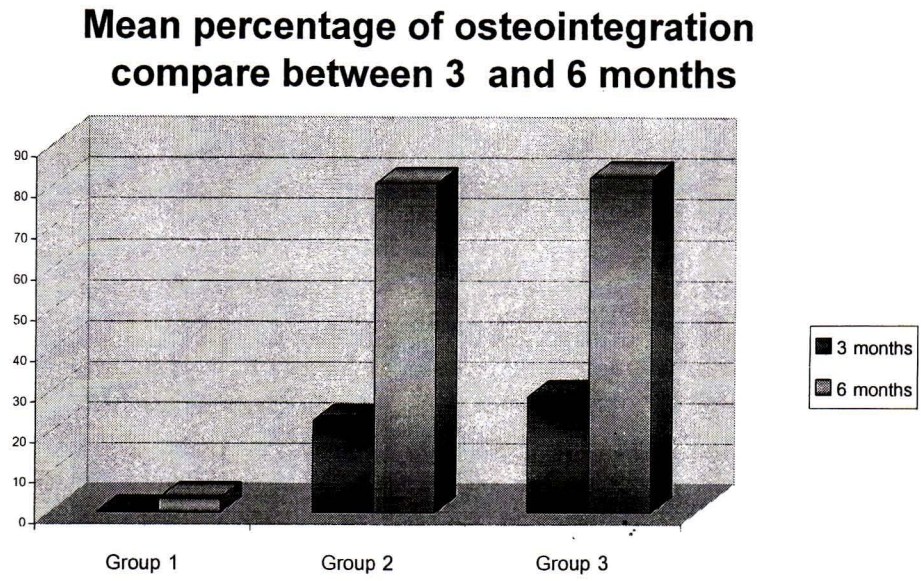

Fig. 4. Showed comparison of osteointegration between 3 and 6 months.

Table 1. Mean percentage of osteointegration at 6 month in each group for osteointegration.

Number	Percentage of osteointegration		
	Group I	Group II	Group III
1	3.56	81.55	82.35
2	3.11	79.22	81.19
3	3.51	80.83	83.45
4	3.51	80.86	81.74
	3.42	80.62	82.18

At 3 months : Group I was different from group II and group III ($p < 0.05$) but not different between group II and group III ($p = 0.458$)
At 6 months : Group I was different from group II and group III ($p < 0.05$) but not different between group II and group III ($p = 0.512$)

significant differences between group II and group III (81.61% *vs* 94.30% : $p = 0.021$) (Fig. 4, 5 : Table 2).

DISCUSSION

Hydroxyapatite is a well-recognized bio-active material and has been used in the improvement of bone-bonding of metallic implants. Because the life span of human beings is quite long, the implants have to be developed, ideally, to sustain life long duration.

Many previous studies concerning hydroxy-apatite coating metallic implants have been reported in clinical situations.

In a matched pair study of 42 uncemented total hip arthroplasty after 3 years follow-up (Mcphersen 1995)[13], hydroxyapatite coated femoral stems demonstrated accelerated bone remodeling, characterized by significantly greater in percentage of cancellous hypertrophy at femoral stem. But this study did not demonstrate any clinical advantage of

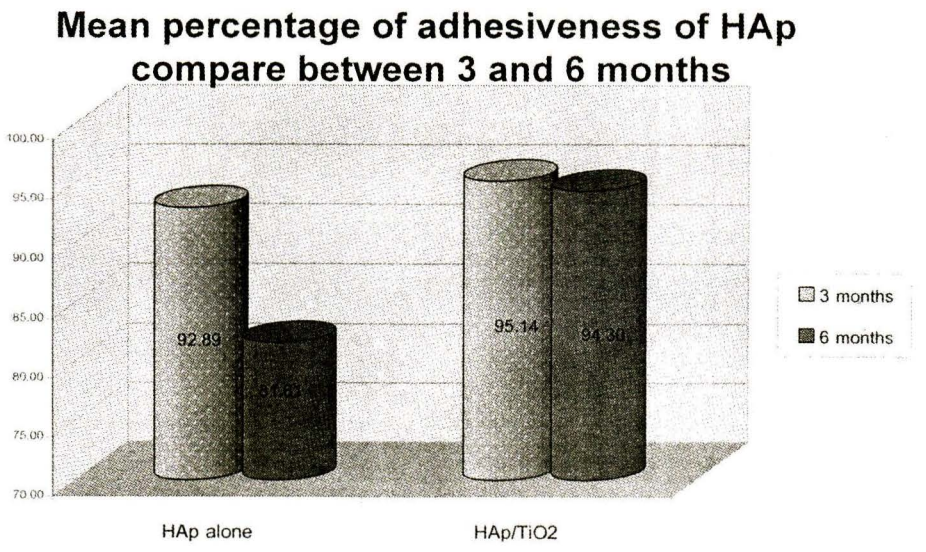

Fig. 5. Showed comparison of adhesiveness of hydroxyapatite (Hap) between 3 and 6 months.

Table 2. Mean percentage of adhesiveness of HAp layer at 6 months compared between with and without TiO2 coat.

Number	Adhesiveness of Hap	
	HAp alone	TiO2/Hap
1	84.09	95.68
2	82.47	92.16
3	80.04	96.73
4	79.84	92.63
	81.61	94.3

For adhesiveness of hydroxyapatite layer
At 3 months : Group II was not different from group III (p = 0.117)
At 6 months : Group II was different from group III (p = 0.021)

hydroxyapatite coating and not known to improve durability of hip arthroplasty.

In a match pair study of 52 total hip arthroplasty after 2.2 years follow-up (Richard 1996)[14], there was no clinical advantage of hydroxyapatite in primary total hip arthroplasty in the short follow-up.

In the study of 152 hydroxyapatite coated femoral prosthesis in total hip arthroplasty after a minimum of 5 years follow-up[15] overall clinical results were excellent in young patients after intermediate term follow-up. Serial radiographs showed mechanically stable implants with osseous ingrowth and minimum endosteal osteolysis.

A study of 124 total hip arthroplasty with hydroxyapatite coating[16] after 6 years follow-up, showed evidence of progressive new bone formation seen at some parts of the femoral stem. Remodeling of the femur began early and low rate of osteolysis was noted.

From clinical studies involving human beings showed that hydroxyapatite coating results in promotion of new bone formation at bone-implant interface. However, the clinical advantage is unclear. Whether this is due to lack of clinical long term follow-up or as a consequence of unforeseen problem during clinical application.

One of the most important clinical problems of hydroxyapatite coating on metallic implants, especially when employing plasma-sprayed technic[2-4] is the poor bonding strength between hydroxyapatite and implant substrate. Since hydroxyapatite melts incongruently as the result of the high temperature presented in a plasma jet it inevitably leads to its thermal decomposition into other calcium phosphates[5,6,17] e.g. TCP, TeTraCP, or non-biocom-

patible calcia- (CaO). The *in vivo* stability of coating is being strongly affected by those decomposition products (Klein 1994)[5].

Application of biocompatible bond coats whose interfacial interactions with hydroxyapatite top coat and Ti alloy substrate provide substantially increased adhesive strength as well as acting as a thermal barrier coating to enhance the crystallinity of deposited bioceramic coating system (Kurzweg 1998, Lamy 1996)[3,6,11]. The interface bond coat/hydroxyapatite is continuous even though a crack has developed along this interface, presumably due to stress introduced during sample preparation. (Heimann 1998)[3].

It has been experimentally shown that the adhesive strength of the system titania bond coat/hydroxyapatite coating as measured by modified peel test (Sexsmith & Trocaynski 1994)[18] increases by 100 per cent compared to Hydroxyapatite coating without a bond coat (42.1 *vs* 21.9 N/m) (Kurzweg 1998)[11] A composite titania/zirconia bond coat increases the peel strength to only 32 N/m (Kurzweg 1998)[19].

Most of the biocompatible bond coatings reported in the literature were *in vivo* studies by immersion in a simulated body fluid (balanced salt solution). There was lack of experimental study in real bone tissue.

The present study was an experimental study in animals which investigated the clearance concerning tissue reaction, bone bonding and hydroxyapatite coating strength between with and without biocompatible coating.

In the present study, hydroxyapatite coating implants group were better than without coating in terms of osteointegration at the bone-implant interface. No difference between hydroxyapatite coating and hydroxyapatite/TiO2 coating was observed in osteointegration, but some crack lines in implants without biocompatible coating group showed an increased chance of adsorption of hydroxyapatite coating due to poor adhesive strength between hydroxyapatite layer and the implant.

In terms of tissue reaction, the addition of biocompatible coating did not provoke any adverse reaction to tissue reaction.

In conclusion, biocompatible coating is one of the alternatives in the improvement of performance of hydroxyapatite coating implant in clinical application. In the present study, results showed a positive trend in improving adhesive strength. However, longer period of follow-up including related biomechanical study is advised.

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การศึกษาปฏิกิริยาเนื้อเยื่อและการชักนำให้เกิดกระดูกใหม่ เปรียบเทียบระหว่างวัสดุโลหะที่ฉาบผิวด้วยไฮดร๊อกซี่แอปาไทต์/ไทเทเนี่ยมอ๊อกไซด์ชนิดต่าง ๆ เมื่อฝังในสัตว์ทดลอง

พิบูลย์ อิทธิระวิงศ์, พบ, อติชาติ พรหมาสา, สพบ**,*
ธาดา ลายประเสริฐ, พบ, ทวีชัย เตชะพงศ์วรชัย, พบ*,*
สมศักดิ์ คุปต์นิรัติศัยกุล, พบ, วรนุช ธนกิจ, พบ***, โรเบริต์ บี ไฮแมน, ปรด*****

วัตถุประสงค์ : เพื่อศึกษาเปรียบเทียบระหว่างวัสดุโลหะไทเทเนี่ยมชนิดที่ไม่มีผิวฉาบ (กลุ่ม 1) ชนิดที่ฉาบผิวด้วยไฮดร๊อกซี่แอปาไทต์ (กลุ่ม 2) และชนิดที่ฉาบผิวด้วยชั้นไทเทเนี่ยมอ๊อกไซด์ระหว่างผิวไทเทเนี่ยมและไฮดร๊อกซี่แอปาไทต์ (กลุ่ม 3) ในแง่ปฏิกิริยาเนื้อเยื่อและการชักนำการเกิดกระดูกใหม่เมื่อฝังในสัตว์ทดลอง

วิธีการ : วัสดุทดลองทั้ง 3 ชนิดถูกนำมาฝังในกระดูกต้นขาส่วนต้นและส่วนปลาย ทั้ง 2 ข้างของสุนัขทดลองแบบกระจาย วัสดุทุกชิ้นมีขนาด 5 x 5 มม^2 ถูกฝังในช่องกระดูกขนาดเดียวกัน สุนัขทดลองได้รับการเอกซเรย์ส่วนขาที่จะได้รับการผ่าตัด ก่อนผ่าตัดและภายหลังผ่าตัด 1, 3 และ 6 เดือน การผ่าตัดเอาชิ้นส่วนวัสดุพร้อมกระดูกรอบข้างออก กระทำภายหลังติดตามผล 3 และ 6 เดือน ชิ้นส่วนต่าง ๆ จะถูกเตรียมเพื่อพร้อมสำหรับการตรวจทางด้านพยาธิวิทยาและด้วยกล้องจุลทรรศน์อิเล็คตรอน ข้อมูลด้านปฏิกิริยาเนื้อเยื่อการเกิดกระดูกใหม่รอบ ๆ วัสดุจะถูกนำมาวิเคราะห์เพื่อหาความแตกต่างระหว่างวัสดุชนิดต่าง ๆ

ผลการวิจัย : ในวัสดุไทเทเนี่ยม (กลุ่ม 1) การตรวจสอบไม่พบการเกิดกระดูกใหม่รอบ ๆ ส่วนวัสดุไทเทเนี่ยมชนิดมีไฮดร๊อกซี่แอปาไทต์ (กลุ่ม 2) พบกระดูกใหม่เกิดขึ้น 25.57% ของพื้นที่ผิวสัมผัส วัสดุชนิดที่มีไทเทเนี่ยมออกไซด์ (กลุ่ม 3) ร่วมด้วย พบกระดูกใหม่เกิดขึ้น 28.63% ในแง่สถิติ ไม่พบความแตกต่างระหว่างกลุ่ม 2 และ 3 หลังแต่สังเกตเห็นว่าผิวฉากไฮดร๊อกซี่แอปาไทต์ในกลุ่ม 2 มีการแตกแยกจากผิวไทเทเนี่ยมในบางส่วนของผิวสัมผัส วัสดุทั้ง 3 กลุ่ม ไม่พบปฏิกิริยาเนื้อเยื่อตอบสนองต่อต้าน

สรุป : การศึกษาพอจะสรุปได้ว่า การมีชั้นของไทเทเนี่ยมออกไซด์ ฉาบระหว่างผิววัสดุไทเทเนี่ยมและชั้นไฮดร๊อกซี่-แอปาไทต์ ทำให้ชั้นไฮดร๊อกซี่แอปาไทต์ ติดยึดแน่นกว่าชั้นไฮดร๊อกซี่แอปาไทต์ ฉาบผิวไทเทเนี่ยมโดยตรงและการฉาบผิวด้วยชั้นไทเทเนี่ยมออกไซด์ ไม่ทำให้การชักนำกระดูกใหม่ต่างไป และไม่มีปฏิกิริยาเนื้อเยื่อตอบสนองต่อต้าน

คำสำคัญ : ไทเทเนี่ยม, ไทเทเนี่ยม/ไฮดร๊อกซี่แอปาไทต์ ฉาบผิว, ไทเทเนี่ยม/ไทเทเนี่ยมออกไซด์/ไฮดร๊อกซี่แอปาไทต์ ฉาบผิว

พิบูลย์ อิทธิระวิงศ์, อติชาติ พรหมาสา, ธาดา ลายประเสริฐ, และคณะ
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* ภาควิชาออร์โธปิดิกส์, คณะแพทยศาสตร์,
** ภาควิชาศัลยศาสตร์, คณะสัตวแพทยศาสตร์,
*** ภาควิชาพยาธิวิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330
**** ภาควิชาแร่วิทยา, มหาวิทยาลัยไฟรเบริก, สาธารณรัฐเยอรมัน