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Analysis of the Postoperative Absorption Process of Unsintered Hydroxyapatite Particles/Poly L-Lactide Composite Device (OSTEOTRANS MX®) for Facial Bone Fractures in 13 Cases

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Abstract

Absorptive devices are often used to treat facial bone fractures in Japan. Only a few reports have investigated whether the plate used was absorbed. In the present study, we used OSTEOTRANS MX® for 13 cases of facial bone fractures at our hospital and studied the progress of the decomposition in the plate body and screw, which required removal due to postoperative infections. OSTEOTRANS MX® was decomposed in the body. The molecular weight of poly-L-lactic acid was reduced and it was finally absorbed; however, unsintered hydroxyapatite was not completely absorbed. In patients in whom the OSTEOTRANS MX® was used, absorption may be completed between 5 to 6 years. However, in certain cases, it takes more than 5 to 6 years. It is necessary to conduct follow-ups until OSTEOTRANS MX® is absorbed and replaced with bone.

Keywords: Facial bones; OSTEOTRANS MX®; u-HA; PLLA; SEM; EDX

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Introduction

Facial bone fractures are often treated using titanium materials. It is said that titanium materials need not be removed after bone recovery because they are non-toxic devices [1-3]. On the other hand, it was reported that titanium has negative effects during long-term use [4,5]. OSTEOTRANS MX® (Teijin Medical Technologies co., Ltd, Osaka, Japan) is a composite absorptive plate of poly-L-lactic acid (PLLA) and unsintered hydroxyapatite (u-HA) particles. It is called Super FIXSORB MX® in Japan. PLLA is a polymer of lactic acid that is present in the human body. u-HA is a calcium phosphate which is a component of in vivo bone and is a type of bioactive bioceramic [6]. OSTEOTRANS MX® is a material that is higher in strength, bioabsorbability, and osteoconductivity than *in vivo* bone. The surface has a small friction coefficient and is non-porous, with little coating formation. It has a unique osteoconvertible character, allowing it to be replaced with autologous bone after 5 years. u-HA is readily visualized under radiation, not only immediately after surgery, but also over time. Biodegradability and absorbability refer to the property that allows the material to be decomposed by body fluids internally. These decomposed substances are metabolized in tissues, absorbed, and finally excreted outside the body. The standard decomposition and absorption process of OSTEOTRANS MX® shows that the decrease in the molecular weight of PLLA after implantation progresses uniformly. The viscosity of the average molecular weight becomes approximately 200,000 or less and low-molecular-weight PLLA will begin to be released. Low-molecular-weight PLLA becomes fine particles, is phagocytosed by histiocytes, and is almost absorbed. In this process, PLLA is decomposed *in vivo* by hydrolysis. It is converted into carbon dioxide and water and is excreted outside the body.

On the other hand, u-HA is absorbed through two different processes. One is biodegradable, in which organic components are absorbed and decomposed by phagocytes such as macrophages and foreign body giant cells. The other is bioresorbable, in which u-HA is absorbed over time

Table 1: Patients with OSTEOTRANS MX® removed due to postoperative infection.

Case	Age	Gender	Diagnosis	Implantation duration
1	62	Male	Multiple facial bone fracture	7 months
2	65	Male	Right side maxilla cancer	1.5 months
3	51	Female	Pharyngeal cancer	1 month
4	40	Male	Zygomatic bone fracture	24 months
5	62	Male	Mandible bone fracture	4 months
6	38	Female	Mandible bone fracture	1 month
7	14	Female	Mandible bone fracture	6 months
8	79	Female	Maxilla bone fracture	30 months
9	43	Male	Zygomatic bone fracture	11 months
10	61	Female	Zygomatic bone fracture	13 months
11	20	Male	Zygomatic bone fracture	54 months
12	56	Female	Orbital floor fracture	13 months
13	80	Male	Zygomatic bone fracture	31 months

by osteoclasts and then converted to bone. Osteoconductivity by osteoblasts to u-HA occurs, osteoclasts are formed, and then u-HA is absorbed. It also exhibits osteo convertibility as a result of bone formation by osteoblasts.

In our hospital, patients using OSTEOTRANS MX® were observed through CT examination in the outpatient department for a period of 5 years, which is the period required for absorption. However, some patients had the device removed due to infections. There are no reports on the decomposition behavior of OSTEOTRANS MX® in the body; however, we report on the decomposition behavior of the plate and screw extracted from the body in cases where removal was necessary in our hospital.

Materials and Methods

Between August 2008 and June 2014, we enrolled 78 cases of OSTEOTRANS MX® (1.0 mm plate, 5 mm or 7 mm screw) implantation due to facial bone fracture or posterior malignant tumor reconstruction in our hospital.

Among them, 13 cases (16.7%) required plate removal since patients experienced complications due to postoperative plate infections. Conservative therapy with antibiotics in these patients did not resolve the infections. The age range at the time of surgery was 14 to 80 years (average, 52 ± 20.1 years), and there were 8 male and 5 female patients. The shortest postoperative extraction of OSTEOTRANS MX® was 1 month and the longest was 4 years and 6 months (average, 16 ± 16.1 months) (Table 1).

Imaging observations with a Scanning Electron Microscope (SEM) and elemental analysis using an Energy Dispersive X-ray spectrometry (EDX) were carried out. In order to judge whether the plate surface deposit is bone or not, the ratio of C/Ca and Ca/P, which is a constituent of bone tissue, was analyzed by EDX. Then, measurement of viscosity average molecular weight by automatic viscometer and measurements of crystallinity by Differential Scanning Calorimetry (DSC) were conducted. Crystallinity was measured since it affects the decomposition rate of OSTEOTRANS MX®.

Results

OSTEOTRANS MX® could not be recognized in cases where it was completely absorbed or replaced with bone, and its shape disappeared. The molecular weight of PLLA decreased with time. Originally, the concentration of the u-HA in the plate was uniform and without pores. However, pores were created when u-HA was released from the plate. It was confirmed that the u-HA was released from the plate pores (Figure 1).

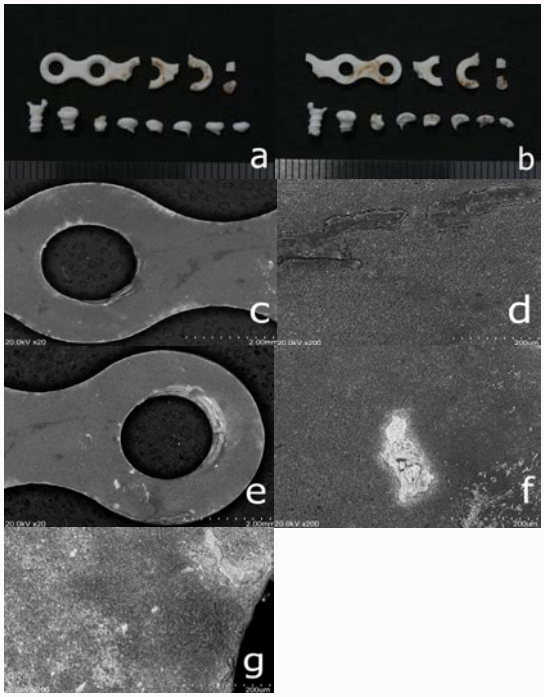

Figure 1: Case 4, a 40-year-old man with left side zygomatic bone fracture OSTEOTRANS MX® for two years.
a: SEM image plate surface after washing with ultrasonic cleaner **b:** SEM image plate back side after washing with ultrasonic cleaner **c:** SEM image before washing (× 20) **d:** SEM image before washing (× 200). A body fluid clot is shown. **e:** SEM image after washing (× 20) **f:** SEM image after washing (× 200). There are fine pores presumed to be traces of u-HA desorption. There is white solid adhesion in the center. **g:** SEM image after washing (× 200). A place with a high white luminance in the left side and a white solid adhering in the right side.

As a result of the measurement of viscosity average molecular weight using an automatic viscometer, the molecular weight of PLLA decreased with time according to the implantation period. It was also

Table 2: Molecular weight and crystallinity of PLLA.

Case	Part	Specimen	Operated months = implantation duration	Molecular weight (kDa)	Crystallinity (%)
1	Orbital	Plate	7	49	55.4
		Screw	7	45	53.7
	Zygomatic	Plate	7	57	52.8
		Screw	7	41	53.4
	Maxilla	Plate	7	54	53.4
		Screw	7	48	53.5
2	Maxilla	Screw	1.5	105	48.8
		Plate	1.5	110	51.2
3	Mandible	Screw	1	143	45.5
		Screw	1	158	47.1
		Plate	1	148	48.6
		Plate	1	151	49.8
4	Zygomatic	Plate	24	18	61
		Screw	24	15	63.5
5	Mandible	Screw	4	60	54.5
		Plate	4	65	55.8
6	Mandible	Screw	1	150	47.7
		Screw	1	123	47.4
		Plate	1	122	51.5
		Plate	1	135	50.7
7	Mandible	Screw	6	44	60.1
		Plate	6	42	56.4
8	Maxilla and zygomatic	Plate	34	11	57
		Screw	34	11	62.8
9	Zygomatic	Plate	11	50	60
		Screw	11	32	61
10	Zygomatic	Plate	13	35	60.5
		Screw	13	25	Uncountable
11	Zygomatic	Plate	54	0.2	Uncountable
12	Orbital	Sheet	23	29	56.7
13	Zygomatic	Screw	31	11	-
		Plate	31	13	-

confirmed that decomposition was smoothly moving along in line with the measurement results of crystallinity by DSC (Figure 2,3 & Table 2).

In addition, bone tissue was not observed on the surface of the plate and the screw, which was in contact with the bone using SEM. When compared with the initial plate before *in vivo* implantation, areas with high white luminance, adhesion of white solids, and fine pores were observed (Figure 1). Component analysis by EDX was carried out on the blackened parts, parts with high white luminance, and parts with adhesion of white solids were observed in SEM (Table 3).

The black part showed a lower u-HA content than the initial plate. In addition, many fine pores were observed. In parts with high white luminance, it was confirmed that the C/Ca value was low. That is, the ratio of Ca was higher in the portion with high white luminance than in the initial plate and bone tissue. The Ca/P in this region was equivalent to that of the initial plate, and the u-HA content was higher than that of the initial plate. In the parts with adhesion of white solids, the solids were found on the surface of the plate and screw and adhered from the outside to the plate surface. The C/Ca value was lower than that of bone tissue; that is, the ratio of Ca was high. In addition, the Ca/P value was equivalent to that of the initial plate.

In case 4, a 40-year-old male underwent invasive repair and fixation with OSTEOTRANS MX® for a left zygomatic bone fracture. Two years after surgery, there was a plate infection of the left frontozygomatic suture and treatment with antibiotics did not alleviate the infection; therefore, the plate and the screw were removed (Figure 1).

Discussion

In animal experiments, it has been reported that the u-HA/PLLA complex shows better bone conduction, and firmly binds to the bone, than PLLA alone during bone surface fixation or intraosseous

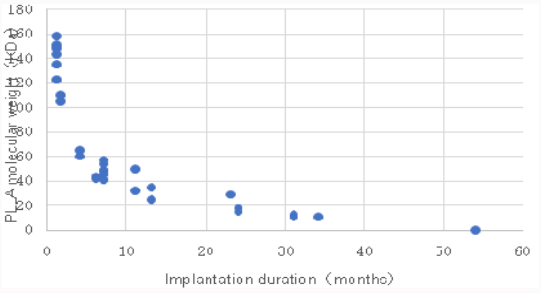

Figure 2: Relationship between OSTEOTRANS MX® filling period and PLLA molecular weight.

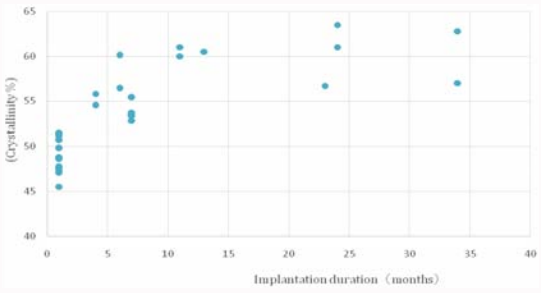

Figure 3: Crystallinity.

Table 3: EDX result of analysis.

Case	Analysis area	Atomic ratio		
		C/Ca	Ca/P	HA content ratio (%)
1	Black part	15.77	1.55	19.6
	High white luminance	3.75	1.52	50.6
	Adhesion of white solids	2.59	1.65	—
4	Adhesion of white solids	1.59	1.6	—
	Black part	14.7	1.58	20.7
	Black part	8.79	1.62	30.4
	High white luminance	4	1.61	49
	Adhesion of white solids	1.18	1.6	—
	High white luminance	3.52	1.54	52.2
5	Adhesion of white solids	0.7	1.42	—
	High white luminance	3.32	1.53	53.3
	Black part	6.42	1.52	32.4
	Adhesion of white solids	0.72	1.39	—
	High white luminance	2.91	1.59	58.3
	Adhesion of white solids	0.87	1.53	—
7	Adhesion of white solids	0.85	1.61	—
	High white luminance	3.56	1.59	—
	Black part	7.75	1.56	27.8
	Adhesion of white solids	1.04	1.66	—
	Black part	8.4	1.68	25.9
	Initial plate	4.93 ± 0.14	1.57 ± 0.03	40
	Rabbit femur	7.17 ± 0.93	1.41 ± 0.04	—

fixation [6,7,8,9]. Bone marrow itself has osteogenic activity; however, it is significantly lower than that of the periosteum or endosteum osteogenic activity. Therefore, the level of bioresorption and bioactivity depends on the proximity of the implant to the endosteum [10]. It is believed that the anatomical location of the material used has a major impact on bone formation and remodeling around the implant. When u-HA is in close contact with cancellous bone, complete replacement of bone occurs [10]. In addition, it was reported that 2 cases of OSTEOTRANS MX® plates were implanted on the infraorbital border and a plate system protruded slightly from the skin surface [11]. This is possible in areas with thin, soft tissue, and where the bone is near the surface of the skin, that a plate system on the bone surface can be palpable. Therefore, a good adaptation of the OSTEOTRANS MX® is as follows: there are no parts that can be palpable on the skin surface in the part of the mandible, maxilla, zygomatic bones, etc. In addition, implants in hairy parts that are slightly protruding would not be noticed because protrusion is hidden by hair [6]. Additionally, titanium miniplates at the frontozygomatic suture had high rates of complications due to visibility, palpability, and thermo-hypersensitivity [12,13,14]. Other studies state that the most commonly removed titanium miniplates were buttress plates [15]. Such prominences incur a risk of infection. Whether PLLA and u-HA are the sources of infections was unclear in this experiment. Follow-up observation was possible because of radiographic imaging and visualization by CT. There was also a report that bone fusion at the fracture site, bone bonding around the plate, and bone replacement were observed on follow-up CT at 13 months after surgery [16].

In our case, postoperative plate infection was observed in 13 cases. A case required plate removal with the longest period of 4 years and 6 months after the operation. As a result of elemental analysis by EDX, u-HA content was low in the black parts as confirmed by SEM, and it was inferred that u-HA was detached from the plate and the part of the plate from where u-HA detached became fine pores. It can also be inferred that bone tissue was bound to biologically active u-HA from an experiment reporting on OSTEOTRANS MX® [10]. In our experiment, it was presumed that the bone tissue did not migrate to the plate due to the force exerted when peeling off the plate. At places with high white luminance, it was inferred that substances close to u-HA derived from the body are deposited. From the *in vitro* test immersed in simulated body fluid, calcium phosphate and u-HA deposits were confirmed on the surface at the early stage of immersion [10]. In addition, it was presumed that the same phenomenon occurred in our study. In parts with adhesion of white solids, we inferred that the white solid matter adhering to the plate was not bone tissue because the white solid adhesion spots had a lower C/Ca value than the bone tissue. From the Ca/P value in this region, it was inferred that substances close to calcium phosphate derived from the body were deposited at a high density and aggregated. Therefore, it was presumed that the deposition of substances observed in the region of high white luminance further progresses and the calcium salt crystallizes.

In our case, the degree of OSTEOTRANS MX® crystallinity, which was 55% or less before insertion in the body, increased with the lapse of time in the body (Figure 3).

Absorption of u-HA was delayed because the plate did not completely adhere to the bone. Meanwhile, as the degree of crystallinity of u-HA advanced and density of u-HA increased u-HA became non-bioresorbable and thus could not be absorbed by osteoclasts.

It is predicted that u-HA crystals grow because the plate does not adhere to the bone completely, and u-HA density increases faster than a plate with complete bone adhesion. As the crystals grow larger and

become denser, it is difficult for osteoclasts to absorb OSTEOTRANS MX®. Although u-HA was originally absorptive, it seems that u-HA became nonabsorbable as it became highly crystalline over time.

Conclusion

There were no cases where the shape of OSTEOTRANS MX® completely disappeared in this study. However, in our previous study, we reported that absorption and bone substitution progressed favorably where the plate is in close contact with the cortical bone as compared with the part distal to the cortical bone [17]. Special skills may be necessary to close and fix the plate. Although PLLA is absorbed within a short time, u-HA requires time for bone replacement, thus, there are many cases with residual u-HA on CT images. Furthermore, u-HA only remains on CT images until its absorption is complete. Thus, it is degraded and absorbed and at least 5 years of CT imaging inspection is needed. Therefore, follow-up observation is necessary.

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