Production and Function of a Novel Percutaneous Device Realizing of Prevention of Germ Infection Made of a Nano-scaled Hydroxyapatite Crystals/polymer Composite

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Statement of Purpose: Various percutaneous devices, such as catheters for intravenous hyperalimention(IVH), have been used in medical fields. However, there has been a serious problem regarding infectious agents enter-ing from the outside through the gap between the skin and the device. To prevent the infection, various materials such as silicone, polyester, collagen, polyurethane, alumina, titanium, tantalum, and hydroxyapatite (HAp) have been applied to percutaneous devices since 1950 but sufficiently good results have not been clinically obtained.

We have been developed a novel inorganic/organic composite aiming at producing a percutaneous device which shows adhesiveness between soft tissue and the composite [1]. Attention in the development of the composite has been placed on the excellent bioactivity of HAp for hard or soft tissues. In this study, a prototype of percutaneous device was made of an inorganic/organic composite consisting of nano-scaled HAp crystals and silk fibroin (SF) via covalent bonding.

Methods: Nano-scaled HAp crystals were prepared by an alternating emulsion system, sintered at 800˚C for 1 h [2]. The size of the HAp crystal was an a-axis length of 87±23 nm, a c-axis length of 236±81 nm, and a mean aspect ratio (c/a) of 2.72. Degummed fibers with 27-denier made of silk from *Bomboxy mori* were used as polymer substrates. Graft polymerization of γ-methacryloxypropyl trimethoxysilane (MPTS) on the SF was conducted by free radical initiation. After the HAp crystals were suspended in ethanol, the poly(MPTS)-grafted SF was soaked in the suspension. The SF adsorbed with HAp was heated at 120˚C for 2 h *in vacuo* for a reaction between the HAp surfaces and the alkoxysilyl groups of the polymer-grafted on SF to donate covalent bonding. A tube-form substrate was made from a silicone compound by molding. HAp/SF fibers of about 100 μm in length were thoroughly coated on the tube. To detect initial cell adhesiveness on the samples, morphologies of fibroblast cells were observed with a scanning electron microscope (SEM). It was performed that the animal experiments with a percutaneous implantation of the catheter with tube-form device(Fig.1) for short to long period.

Results / Discussion: The weight gain of poly(MTPS) on SF increased with increasing the reaction time, eventually reached a plateau value of about 15 wt%. The amount of the HAp bonded on the SF fiber was 13.1 wt%, which was 5 times larger than that on the SF fabric (2.8 wt%) under the same conditions. This means that it is hard for the HAp crystals to penetrate into the gaps between fibers in the fabric. The HAp crystals were bonded as aggregates, which is because a HAp crystal consists of an a-plane with a cationic charge and a c-plane with an anionic charge.

To fabricate a prototype of a percutaneous device, the HAp/SF composite fibers were transplanted onto a tube-form substrate made from a silicone via an adhesive agent. The HAp/SF composite fibers of 100 μm in length could be transplanted uniformly and individually in random directions on the tube. To evaluate the cell adhesiveness on the HAp/SF composite, the morphologies of L929 fibroblast cells incubated on the sample fabric or devices were observed by SEM. It is clear that cells favorably adhere only on the HAp surface of the composite but not on the dehydrated graft-surface without HAp crystals on the SF substrate. It is estimated that cell-adhesion proteins in serum, such as fibronectin, vitronectin, bFGF, etc., adsorb on the HAp surface much better than on the dehydrated graft-poly(MTPS). To evaluate the skin tissue adhesiveness on percutaneous device, the catheter with percutaneous device was implanted percutaneously. The result of the animal experiments was shown that the skin tissue adhered well in short period, and to be not able to detect abscess at least 25 months.

Conclusions: Nano-scale HAp crystals were covalently bonded to the surface of the SF substrate through poly-(MTPS) grafting on the substrate. The HAp coating was effective for improving the adhesiveness of the fibroblast cells. A tube-form percutaneous device was fabricated by transplanting the HAp/SF composite fibers of about 100 μm in length onto the surface of a tube made from a silicone compound via an adhesive. The device was white and had good flexibility. Cells were able to penetrate into the space among the composite fibers in three-dimensional tangle. Skin tissue is expected to behave in a manner similar to the penetration of the cells into the device. And the device realized the infection-protection properties from adhesiveness to skin tissue for 25 months.

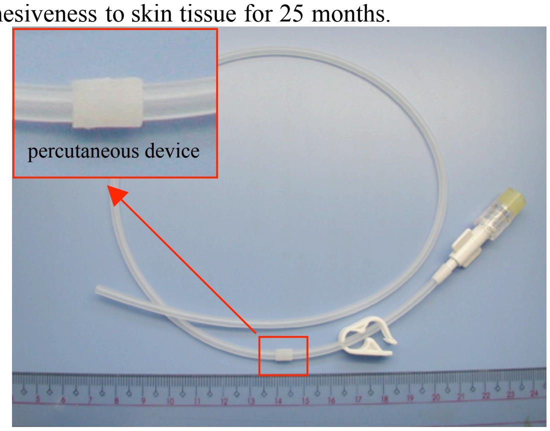

Fig. 1 A photograph of the catheter with percutaneous device made of HAp/SF composite fibers.

References: [1] T. Furuzono, S. *et al.*, *J Artif Organs*, 2004;7: 137-144. [2] T. Furuzono *et al., J Mater Sci Lett,* 2001;**20**: 1205-1212.