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Author(s)	Shimozuru, T.; Kamezawa, T.; Kuratsu, J. et al.
Citation	Interventional Neuroradiology. 2004, 9, p. 29-33
Version Type	VoR
URL	https://hdl.handle.net/11094/50290
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Hydroxyapatite and bFGF Coating of Detachable Coils for Endovascular Occlusion of Experimental Aneurysm

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Key words: experimental aneurysm, embolization, hydroxyapatite, bFGF

Summary

The purpose of this study was to evaluate the effect of hydroxyapatite (HAp) and fibroblast growth factor-basic (bFGF) coating on Guglielmi detachable coils (GDCs) in an experimental aneurysm model. A total of 18 aneurysms were experimentally made in the common carotid arteries of swine. Embolization was done on these aneurysms using standard GDCs and coated GDCs with HAp (GDC-HAp) and with bFGF (GDC-HAp-bFGF). The animals were then killed 14 days after embolization. The development of tissue scarring and coverage the aneurysm's orifice were evaluated macroscopically. No significant difference of volume ratio of the coils existed in each group. Macroscopically, covering ratio of fibrous membrane at the neck of aneurysms were $88.3 \pm 14.7\%$ in a group with GDC-HAp-bFGF, while it were $26.7 \pm 15.3\%$ in a group with standard GDC and it was $41.7 \pm 31.7\%$ in a group with GDC-HAp. These results indicated that coating by hydroxyapatite and bFGF might facilitate a wound healing in an experimental aneurysm model.

Introduction

Several studies dealing with long-term angiographic and histopathologic examinations showed that the treated aneurysms developed

coil compaction and recanalization and coverage across the neck of the aneurysm was not recognized^{1,3,7}. In our previous study, coils coated by HAp might enhance intra-aneurysmal scar formation and re-endothelialization across the neck of aneurysm¹⁰.

Platinum coils were inert and not cell-adhesive. Hydroxyapatite is a biological carrier with enhancement of thrombus organization, and basic FGF is a potent mitogenic agent for wide variety of mesoderm-driven cells including fibroblast, capillary and endocardial endothelial cells, smooth muscle cells. Apatite formation on/in hydrogel matrices were developed using a novel alternate soaking process¹². This study was designed to check the hypothesis that embolization with coating coils develops endothelialization across the neck in an experimental intracerebral aneurysm model of swine.

Material and Methods

1) Coil Coating

GDC, sizes 18 (6-20 cm length, 3-8 mm helix diameter, platinum coil with 0.015 inches thickness; Boston Scientific Corp., Fremont, CA) was used for embolization. Hydroxyapatite coating method was reported previously. The GDC-HAp were immersed in a solution con-

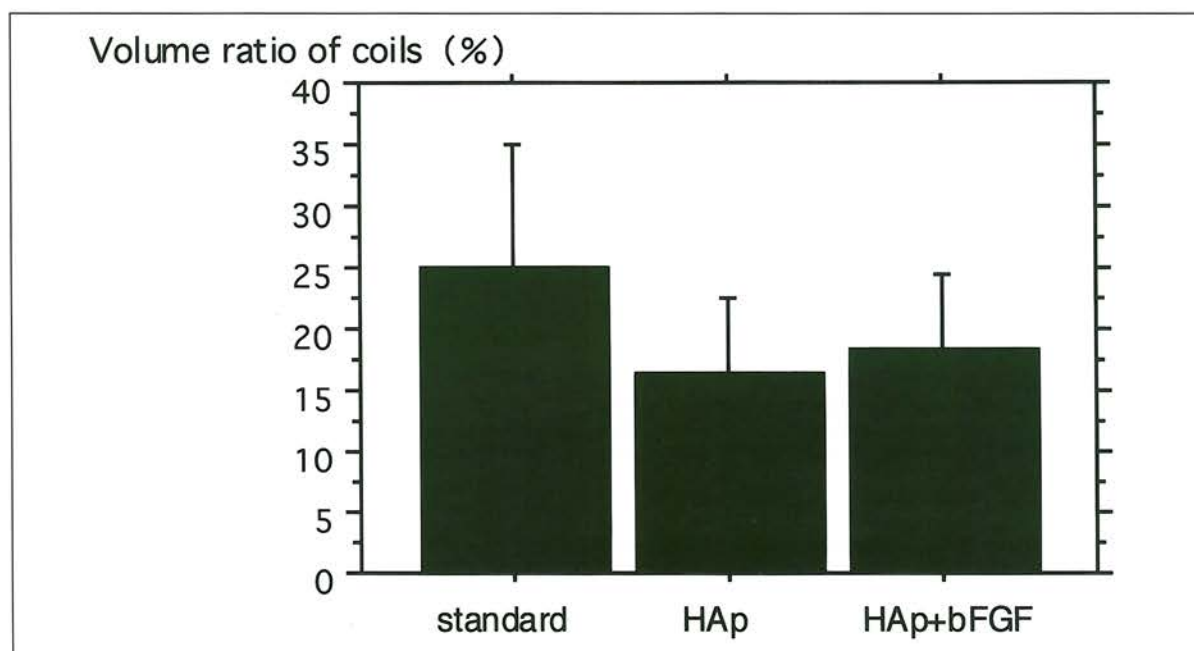
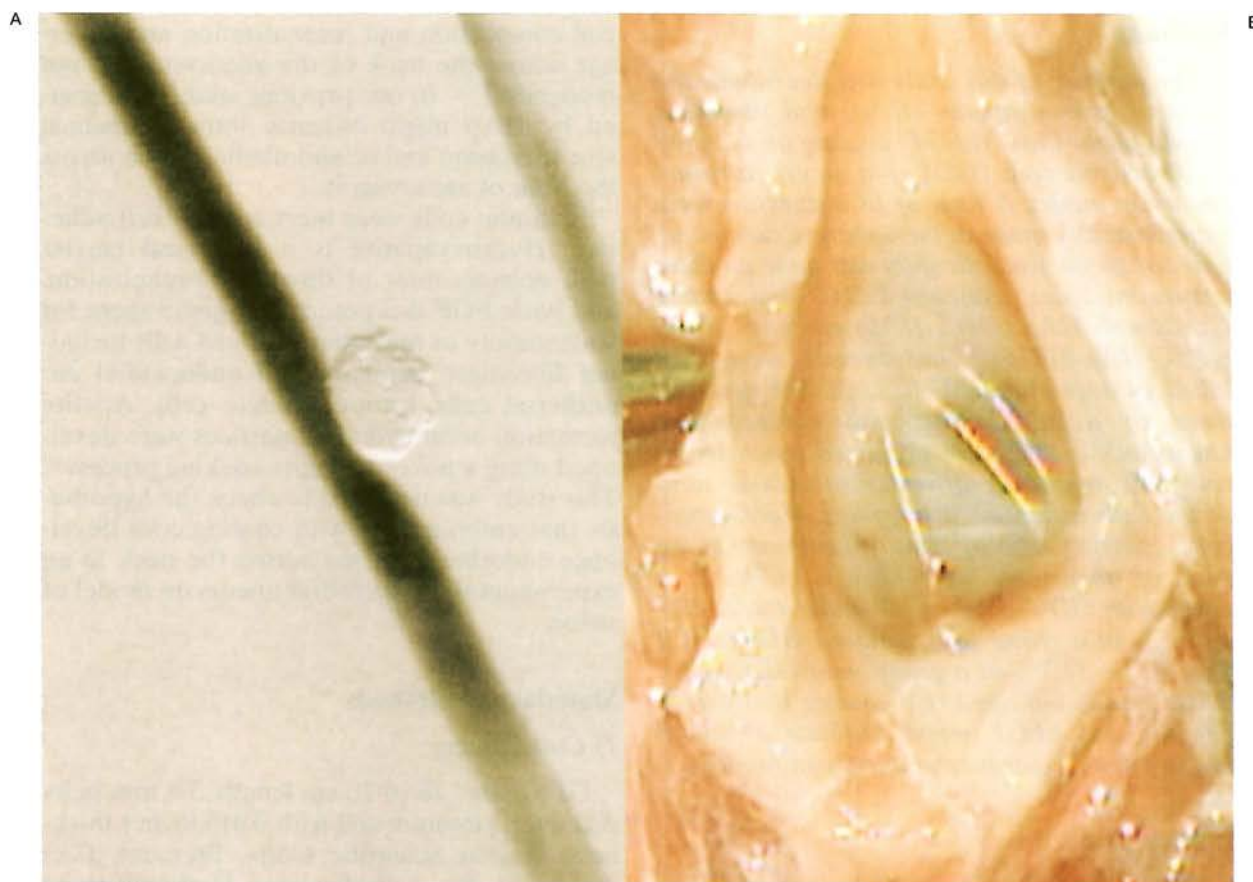


Figure 1 Volume ratio of coils in each groups.



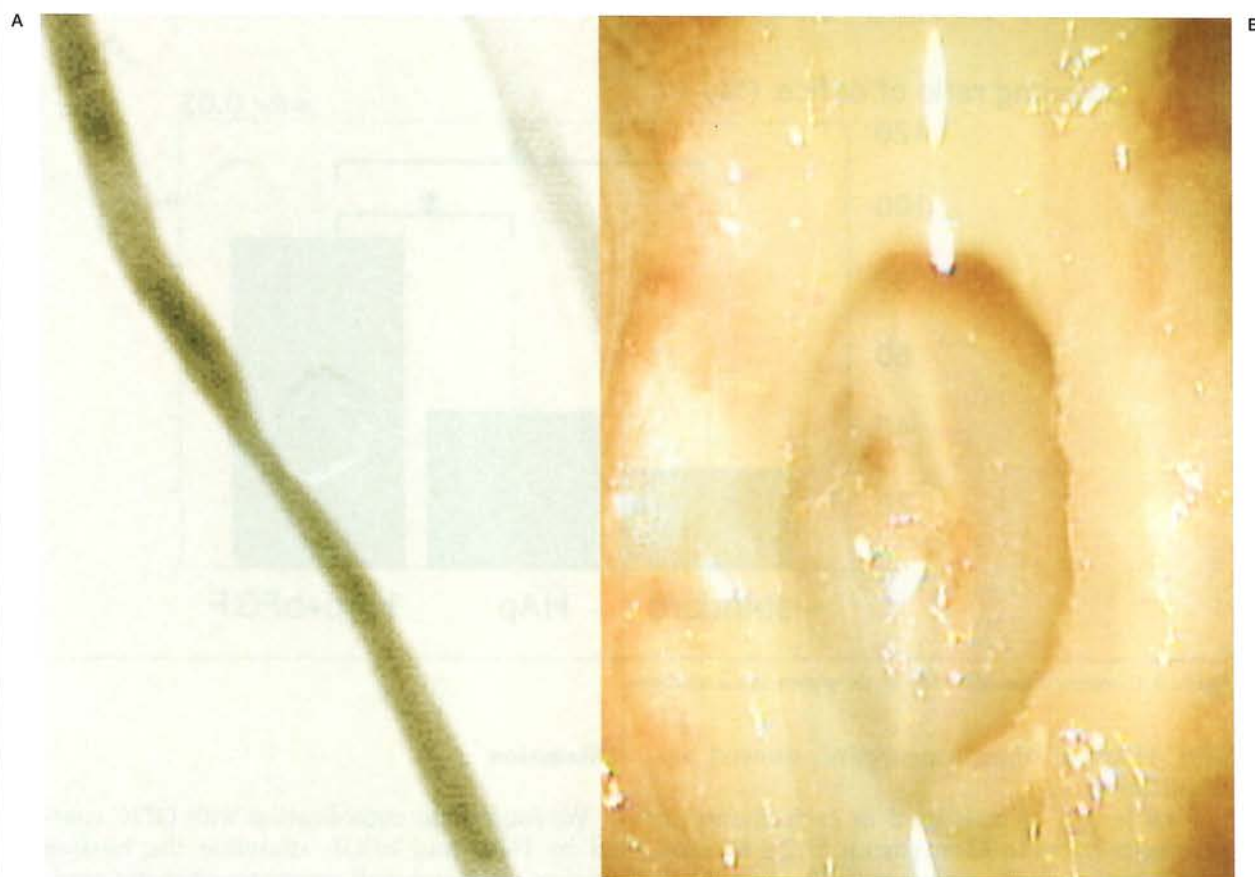


Figure 3 A) Angiograms of experimental aneurysms embolized by GDC-HAp-bFGF. Complete occlusion was recognized 2 weeks later. B) Macroscopic appearances of an aneurysmal orifice. The orifice of aneurysm was covered completely with thick fibrous tissue.

taining 1 μ g/ml recombinant human bFGF (Sigma Corp, St. Louis, USA) during 20 minutes before embolization.

2) Aneurysm Construction and Coil Embolization

The details of aneurysm construction and coil embolization have been reported¹⁰. A total of 18 saccular aneurysms with 5 mm in neck and 6 to 8 mm in length were experimentally made in bilateral common carotid arteries of nine swine using a microsurgical technique. GDCs were placed in the lumen of the aneurysm until no additional coils could fit into the aneurysm.

3) Final Angiographic and Histopathologic Studies

Final angiography was performed before killing animals to document the radioanatomical results. Then the aneurysm-parent artery

complex was removed and parent artery of the specimens were cut from the bottom to the orifice and direct view of aneurysm orifice and coil surface was obtained and photographically documented.

Results

1) Angiographical Studies

Embolization was performed for 18 aneurysms.

Fourteen days after embolization, three aneurysms had parent artery occlusion and thrombus formation from orifice to parent artery. Angiographic examination in 15 aneurysms were done. Two of three aneurysms embolized by standard GDCs and five of six aneurysms used by GDC-HAp and all GDC-HAp-bFGF demonstrated nearly total occlusion (figures 2,3). One standard GDC and one

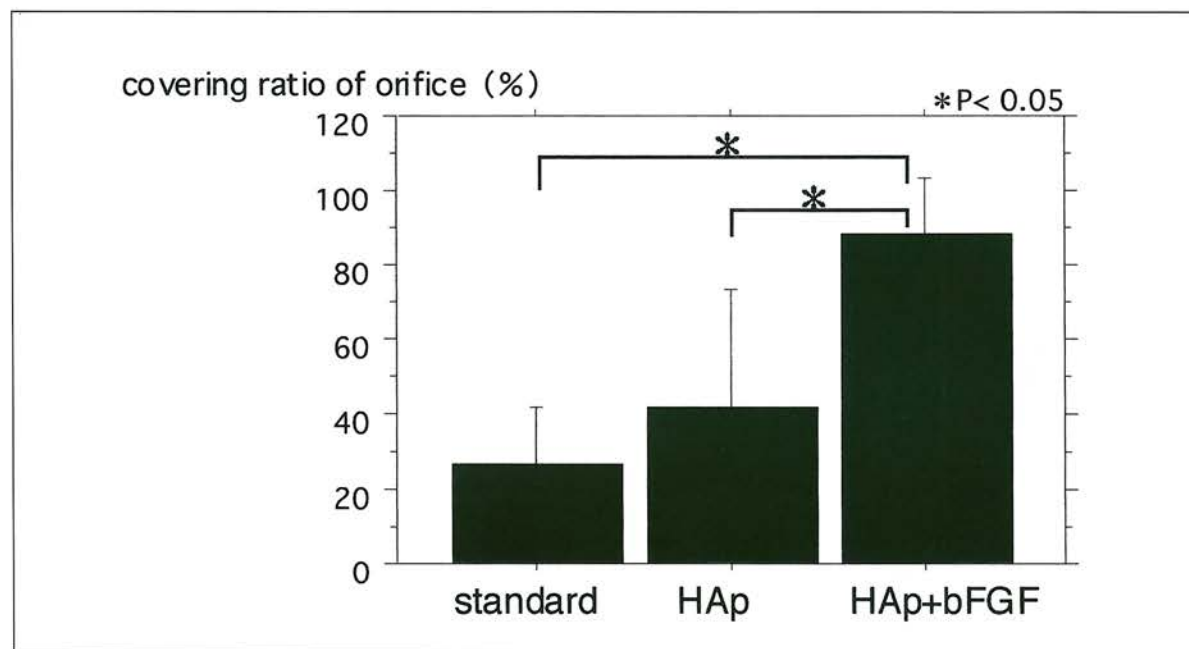


Figure 4 Covering ratio of orifice of aneurysms in each groups.

GDC-HAp of these aneurysms showed recanalization.

Total length of coils used in each aneurysm were from 28 cm to 72 cm (mean, 51.2 ± 6.2 cm), volume ratio of coils with respect to aneurysmal volume were approximately 18.5% to 25%. Significant difference of volume ratio of the coils in each groups was not recognized (figure 1).

Volume ratio of coils; Length of coils \times (coil radius) $2 \times \pi$ / sac volume

2) Macroscopic Findings

Macroscopic examinations of the aneurysms showed significant differences between the standard GDC and GDC-HAp-bFGFs. The surface of the standard GDCs was covered with a thin fibrin-like white material. On the other hand, a denser and thicker fibrous tissue was observed at the neck of aneurysms embolized with GDC-HAp-bFGFs (figures 2,3). The predominantly fibrous scarring was covered with neoendothelium arising from the edges of the neck of the aneurysm. Covering of fibrous membrane in the orifice was 26.7% of the aneurysms embolized by standard GDCs, $41.7 \pm 31.7\%$ of those by GDC-HAps, $88.3 \pm 14.7\%$ of those by GDC-HAp-bFGF (figure 4). There was statistically significant difference ($P < 0.05$) between standard GDCs and GDC-HAp-bFGF.

Discussion

We found that embolization with GDC coated by HAp and bFGF stimulate the healing process of lateral wall aneurysm of swine model. Fibrous membrane covering of neck were recognized in GDC coated by HAp and bFGF, compared with of standard GDCs.

Several studies have stated that important anatomic limitations on complete occlusion associated with this endovascular therapeutic procedure^{1,6,13}. Platinum is inert biologically and does not elicit a significant biological response on its surface. Coating on platinum with proteins might be difficult, by polyester fiber⁵ collagen cores², incorporating collagen thread¹¹, ion implantation with fibronectin, laminin⁸ to modify coil thrombogenicity and inflammatory cellular response.

In this study, we used GDCs coated by HAp which enhance thrombogenicity and bFGF which promote neointimal hyperplasia in the healing process of aneurysm.

There are several limitations in our study. Lateral side wall aneurysm in the swine has a strong tendency for spontaneous wound healing. Owing to apprehension of the excess thrombogenicity of HAp, we performed strict heparinization and anti-platelet drugs similar to clinical procedure¹⁰. Three of 18 aneurysms em-

bolized had parent artery occlusion. Thrombogenicity play an important role in the first stage of wound healing and then ECM and basic Fibroblast growth factor (bFGF) play same role in second stage^{9,14}.

Some studies have examined the effect of various proteins on SMC proliferation, attachment, and the growth of endothelial cells derived from artery wall¹³. In second limitation, We used infiltration of GDC-HAp into a solution containing 1µg/ml bFGF. But, activity of bFGF is very short. We reported histologic changes in aneurysms embolized with GDCs-HAp in the early stage¹⁰. Coating of surface GDC-HAp using other proteins such as bonding with bFGF, may be of value in late stage of complete aneurismal occlusion.

Conclusions

GDCs coated by HAp and bFGF show a faster neoendothelial proliferation in the aneurysm neck.

Such promoted biological response may decrease the chances of coil compaction and recanalization in human cerebral aneurysms treated by GDCs.

Acknowledgements

The authors acknowledge the technical assistance of R. Uemura, H. Kanetsugi, K. Kawaguchi, K. Kori, N. Komaki, Technical Research Center of Boston Scientific Co., Miyazaki, Japan.

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