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ORIGINAL ARTICLE

Histopathological differences of experimental aneurysms treated with bare platinum, fibered, and bioactive coils

Yoko Usami[a], Naoki Hirokawa[a], Masato Saitoh[a], Hiroki Okuda[a], Masanori Someya[a], Tadashi Hasegawa[b], Yasunari Takakuwa[c] and Koh-ichi Sakata[a]

[a]Department of Radiology, Sapporo Medical University, Sapporo, Japan; [b]Department of Surgical Pathology, Sapporo Medical University, Sapporo, Japan; [c]Department of Surgical Pathology, NTT-East Sapporo Hospital, Sapporo, Japan

ABSTRACT

Purpose: To evaluate the histopathological features of experimental aneurysms embolized with bare platinum, fibered, and bioactive coils.

Material and methods: Twelve experimental aneurysms were constructed in three swine. The aneurysms were divided into four groups and were embolized using a bare platinum coil alone (P group, $n = 2$), a bioactive coil alone (B group, $n = 2$), a combination of fibered and bare platinum coils (F/P group, $n = 4$) and a combination of fibered and bioactive coils (F/B group, $n = 4$). Histopathological data for all aneurysms recorded at 63 days were analyzed in terms of neointima formation, fibrosis, foreign-body giant-cell infiltration, and organization.

Results: Fibrosis was significantly greater in group B compared with that in group F/P ($p = .02$). Inflammation with foreign-body giant-cell infiltration was significantly greater in groups F/P and F/B compared with that in groups P and B ($p = .007$).

Conclusion: The present study revealed that the embolic effect of fibered coils was not a thrombus but instead was a foreign-body response in the chronic phase.

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KEYWORDS
Coil embolization; fibered coil; bioactive coil; histopathological features

Introduction

Transcatheter embolization in peripheral vessel diseases has become widely used as a less invasive therapeutic alternative to open surgery [1–3]. However, recurrence after coil embolization, including coil compaction and recanalization, remains problematic.

Various types of coils, including bare, fibered, bioactive and hydrogel coils, are available for coil embolization, and each type of coil has different physical and biologcal properties [4–6]. Few studies have described the clinical outcomes of coil packing for visceral arterial aneurysms (VAAs), and most of these studies involved treatment with bare platinum coils [3]. No report has shown which type of coil is best to use in peripheral vessel disease. For these reasons, it is difficult to determine the optimal kinds of coil use in various situations.

Embolization without recurrence requires physical stabilization and histopathological cure of the embolic sites. The high volume embolization ratio and the mechanical stability of coils contribute to the physical stability of the embolic sites [3,7]. Histopathological cure consists of a fibrotic change in embolic sites [8]. Evaluation of the histopathological features reflecting the biological effect is essential for understanding the healing mechanisms of aneurysms. Reports referring to the histopathological differences associated with coil embolization mainly involve cerebral aneurysms [4–6,9], while there is only one report addressing the type of fibered coils commonly used in peripheral arteries.

A novel strategy should be explored for embolization of peripheral regions, which are larger and more amorphous than cerebral aneurysms. These strategies should reduce the rate of recurrence and number of coils and preserve the function of the peripheral organ. Our clinical experience has shown that a combination of a fibered coil and a bioactive coil is useful. Therefore, we performed histopathological analyses of each coil group as a first step.

The purpose of this study is to compare the histopathological features of experimental aneurysms embolized with bare platinum, fibered, and bioactive coils.

CONTACT Y. Usami usayo@sapmed.ac.jp Department of Radiology, Sapporo Medical University, School of Medicine, S1W16, Chuo-Ku, Sapporo 060-8543, Japan

Material and methods

All animal procedures were conducted in compliance with relevant guidelines and received approval from the institutional animal care committee. We used three Duroc swine (−13–16 weeks; 40–47 kg) in this study.

Anesthesia

The swine were anesthetized with ketamine (5 mg/kg) and medetomidine (80 μg/kg) administered via the intramuscular route. The animals were then intubated and maintained on 1.5–2.2% isoflurane, with 3.0–4.3% inhaled nitrogen monoxide administered to effect, in 100% oxygen, at 2.7–4.0 L/min. Heart rate, respiratory rate, temperature, oxygen saturation, and end-tidal CO_2 were monitored during anesthesia. A 5000-U bolus of heparin and additional doses were administered to achieve an activated coagulation time >200 s, measured at one-hour intervals.

Experimental aneurysm construction

After the preoperative preparation described above, 12 experimental lateral-wall aneurysms were constructed in three swine as previously described by Murayama et al. [10].

Embolic devices

We chose 0.010-inch coils to achieve complete occlusion in the embolization of small (approximately 5 mm) aneurysms.

The bare platinum coil devices used in this study were a GDC 360° 0.010-inch device, a GDC Helical 0.010-inch device, and a Target 360° 0.010-inch device (all from Boston Scientific, Natick, MA, USA). The bioactive coil devices employed were a Matrix2 360° 0.010-inch device and a Matrix2 Helical 0.010-inch device (both from Boston Scientific). The fibered coil device employed was a Vortex 0.018-inch device (Boston Scientific).

Embolization procedure

Following aneurysm construction, aneurysmal embolization was carried out by two experienced interventional radiologists with over ten years of experience. Twelve aneurysms were embolized with bare platinum coils (P group) ($n = 2$), bioactive coils (B group) ($n = 2$), a combination of fibered and bare platinum coils (F/P group) ($n = 4$) or fibered plus bioactive coils (F/B group) ($n = 4$). Clopidogrel (75 mg, p.o.) and acetylsalicylic acid (81 mg, p.o.) were administered once daily from postoperative day 1 throughout the treatment period.

A 7-Fr sheath was placed in the right femoral artery under sterile conditions, and a 7-Fr guiding catheter (Guider; Boston Scientific) was advanced into the common carotid artery for the balloon-assist technique using a single-vessel approach. Then, selective angiography was carried out. We measured aneurysm dimensions using three-dimensional digital subtraction angiography (3D-DSA). Aneurysm volume was determined from the width, height, and length measurements recorded before embolization. The aneurysms were assumed to be cylindrical, and their volume was determined based on the following equation:

$$\text{Volume} = 4/3 * \pi * (\text{Width}/2) * (\text{Height}/2) * (\text{Length}/2)$$

The volumes of the devices were determined through *ex vivo* measurement. Theoretical volumetric occlusion was determined according to aneurysm volume.

Embolization was performed under fluoroscopic guidance. We placed a microcatheter (Excelsior 1018; Stryker, Fremont, CA, USA) in the center of the aneurysm and embolized the aneurysm using a balloon-assisted technique routinely, to prevent coil-loop protrusion. A micro-balloon catheter (Sentry 10 mm from Boston Scientific/Target (Fremont, CA, USA); Logos 12 mm from Piolax, Yokohama, Japan) was also used. All aneurysms were framed using 360° coils, followed by filling using helical coils.

In group F/B, the aneurysms were framed with Matrix2 360° coils, followed by packing with fibered coils and finishing with Matrix2 coils. All aneurysms were embolized as completely as possible while minimizing the protrusion of embolic devices into the parent artery.

Follow-up angiography

For follow-up, all swine were anesthetized, and a 5-Fr sheath was placed in the right femoral artery. Follow-up imaging evaluations were carried out on day 63 after deep sedation and euthanasia. We evaluated the effects of occlusion based on the Raymond Scale (complete occlusion (CO); neck remnant (NR); body filling (BF)). We also confirmed the presence of coil loops in each aneurysm. The number of coils was also recorded.

Histopathological analysis

After follow-up angiography, we removed the aneurysms surgically with the surrounding tissue *en bloc*. The tissues were preserved in formaldehyde, embedded in unsaturated polyester resin, and sliced with a precision-cutting machine fitted with a diamond blade. Transverse sections were removed from the middle of the aneurysms, ground to a thickness of ≈100 µm, and stained with hematoxylin and eosin.

The thickness of the neointima tissue covering the neck of the aneurysm as well as areas of fibrosis, infiltration of foreign-body giant cells, and organization were evaluated using NIS-Elements software (Nikon, Tokyo, Japan). Neointima thickness was measured at three points: on both sides and in the middle. The proportions of the tissue area filled by fibrosis, foreign-body giant-cell infiltration, and organized tissue with lymphocytic infiltration were determined as follows:

Fibrosis, foreign-body giant-cell infiltration, or organization area/(aneurysm area – coil area) × 100 (%)

All slides were examined by two pathologists from different medical institutes. These histopathological findings were compared between groups regarding the presence of neointima, fibrosis, foreign-body giant-cell infiltration, and organization. Characteristic findings were also noted if observed.

Statistical analysis

The results were analyzed using SPSS v21 (IBM, Armonk, NY, USA). Comparisons between the four groups were performed using the Kruskal-Wallis test, with Bonferroni's correction for multiple comparisons. $p < .05$ was defined as significant.

Results

Procedural and angiographic results

All three swine survived the surgical and endovascular procedures, and embolization and angiography were completed successfully in all 12 aneurysms. The volumes of the aneurysms, volume embolization ratio (VER), the number of coils and angiographic results recorded after 63 days are shown in Table 1. There were no significant differences in volume embolization ratio (VER), aneurysmal volume or the number of coils between the groups. CO was achieved at follow-up in all four groups. Coil loops were visible in four coil loops in four aneurysms.

Histopathological outcomes

Fibrosis was significantly greater in group B compared with that in group F/P (Figure 1). Inflammation with foreign-body giant-cell infiltration was significantly greater in groups F/P and F/B compared with that in groups P and B ($p = .007$) (Figure 1).

Fibrosis was detected on the sides of the necks of all aneurysms (Figure 2). Phagocytosis of foreign-body cells was detected in groups F/B and F/P (Figure 3), and inflammation with foreign-body giant-cell infiltration was more visible around the fibers in groups F/B and F/P (Figure 4). There was no significant difference in neointima thickness, organization with lymphocytic infiltration between the groups. Unorganized thrombosis was not visible around the fiber and was observed in a very limited area only on one slide, in group F/B.

The rest of the space (except for the coil, fibrosis area, foreign-body giant-cell infiltration, and unorganized thrombotic areas) showed organization and lymphocytic infiltration.

Table 1. Aneurysmal characteristics and angiographic results.

Group of coils	Breeding period (day)	Volume (mm^3)	VER[a] (%)	VER (Fibered coil) (%)	Number of coil	Angiographic result 0 days	Angiographic result 63 days	Coil loop 0days	Coil loop 63 days
P 1	63	76.2	51.7	0	13	CO	CO	0	0
P 2	63	44.2	50.3	0	6	CO	CO	1	1
B1	63	69.7	35.9	0	6	CO	CO	0	0
B2	63	46	40.5	0	4	CO	CO	0	0
FP1	63	39.4	44.1	5.5	3	NR	CO	1	1
FP2	63	61.3	31.4	19	5	CO	CO	0	0
FP3	63	91.6	18.6	10.3	4	NR	CO	0	0
FP4	63	47.3	35.4	20	4	CO	CO	0	0
FB1	63	143.1	34.3	9.2	11	NR	CO	0	0
FB2	63	125.8	26.8	6.4	8	CO	CO	0	0
FB3	63	50.8	48.6	11.5	6	CO	CO	1	1
FB4	63	61.21	25	7.1	3	CO	CO	1	1

[a]Volume Embolization Ratio.

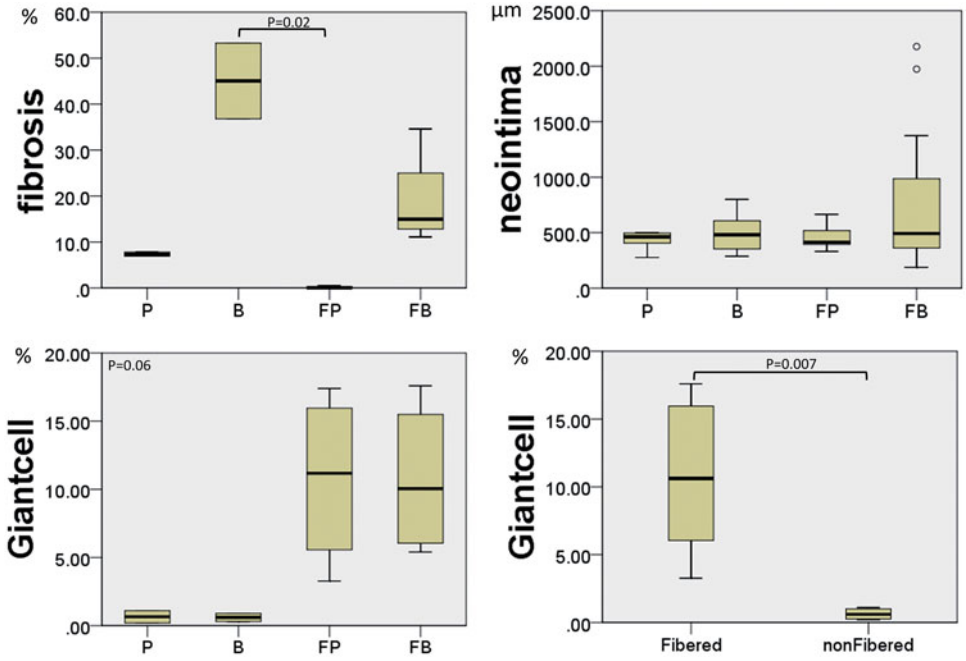

Figure 1. Graphs showing differences in the four groups with regard to neointima thickness and the percentages of the fibrotic area and the area of inflammation with foreign-body giant-cell infiltration.

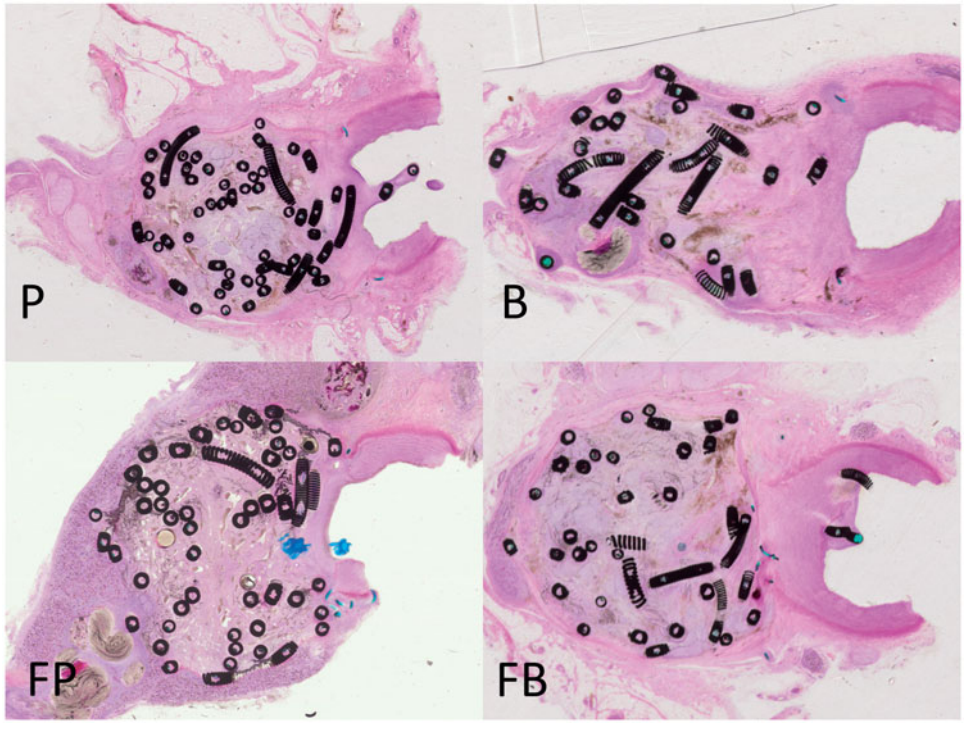

Figure 2. Low-magnification microscopic images after 63 days. Fibrosis development on the side of the neck.

Discussion

We compared the histopathological features of the aneurysms in swine embolized using different types of coils (P, B, F/P, F/B groups) to increase our understanding of their effects on VAAs or peripheral vessels. The results showed that fibrosis was significantly greater in group B, while inflammation with foreign-body giant-cell infiltration was significantly greater in groups F/P and F/B.

The healing process of aneurysms and damaged vessels is considered to share common features with

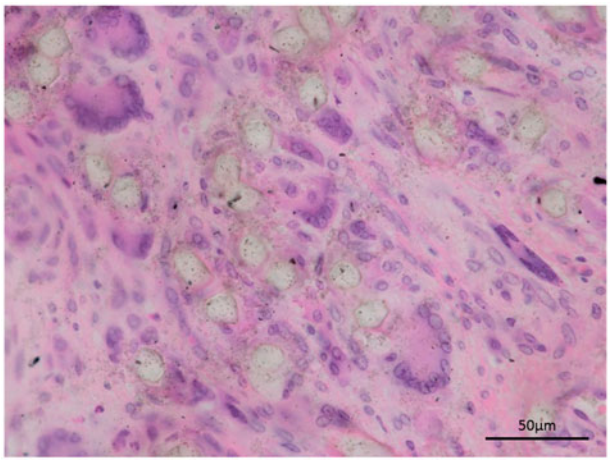

Figure 3. High-magnification microscopic images of group F/B after 63 days. Phagocytosis of foreign-body cells is observable.

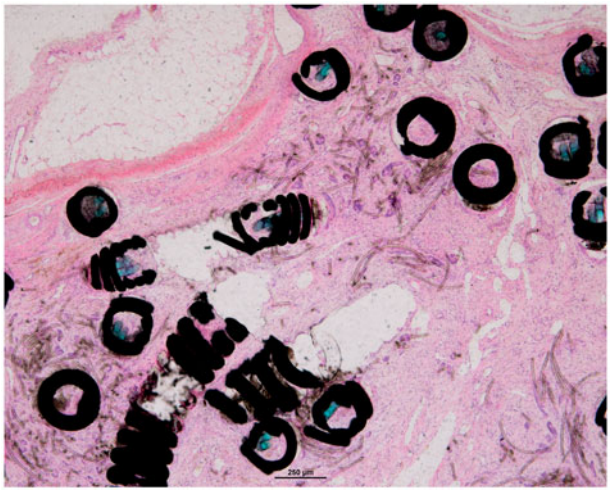

Figure 4. High-magnification microscopic images of group F/B after 63 days. Inflammation with foreign-body cell infiltration around the fiber is observable.

the wound-healing process. In wound healing, thrombus occurs in the damaged area (step 1); neutrophil and lymphocyte infiltration occurs (step 2); granulation tissue consisting of macrophages, neovessels, and fibroblasts is formed (step 3); and the lesion is finally filled with fibrosis (step 4) [11]. The necessary and sufficient histopathological conditions after coil embolization without recurrence are thought to consist of fibrosis in the aneurysmal sac and neoendothelialization of the aneurysmal neck [7,12]. In one study, aneurysms caused by coil embolization without recurrence for 20 years showed an adequate intima, consisting of dense collagenous tissue, and sufficient fibrosis in the sac [8]. Evaluation of histopathological features is considered important for understanding the healing mechanism of coil embolization.

Pathological differences in bare platinum coils, hydrogel coils and bioactive coils have been evaluated. Bioactive coils induce more of a tissue inflammatory response. Bare platinum coils and hydrogel coils are more biologically inert and induce a limited inflammatory response [7]. Bioactive coils accelerate aneurysm fibrosis and neointima formation [4,5]. There is one clinical study showing that fibered coils increase the rate of vessel occlusion and are more effective than standard pushable coils in terms of the clotting effect of the fibers on the microcoils [13]. The effect of fibered coils in the acute phase is a thrombus [14]. However, as far as we know, there is no report to investigate the chronic effects of fibered coils.

In our study, the fibrosis area was more prominent in group B than that in the other groups. This result is in line with the above reports and means that bioactive coils effectively accelerate the inflammation and healing process. However, in clinical situations associated with intracranial aneurysms, there is no evidence that bioactive coils are more beneficial than other types in the long term [15]. In our experiments, we focused on the verification of the biological response of the aneurysms. For this reason, we created a sidewall aneurysm free of hemodynamic stress. This is one of the reasons for the differences between our results and previous clinical studies. To improve the long-term outcome of coil embolization, especially in the clinical setting, it is important to consider biological modifications as well as hemodynamic stress in the targeted vessel and the mechanical stability of the coils. Although a statistically significant difference was not found, the fact that fibrosis was more visible in the F/B group than that in the F/P group may suggest that the bioactive coils can affect fibrotic change even if the fiber is mixed.

Foreign-body giant-cell infiltration was greatest in groups F/B and F/P. Furthermore, inflammation associated with foreign-body giant-cell infiltration was more visible around the fibers in these groups, and phagocytosis of foreign-body cells was also detected. Our results revealed that embolization with fibered coils did not create clots but did cause foreign-body giant-cell infiltration after 63 days. This result suggested the embolic effect of coils in the chronic phase may be affected more by the inflammation associated with giant-cell infiltration than the platinum coils and unorganized thrombus. It can be assumed that the foreign-body reaction appears because the fibers attached to the coils consist of non-absorbable polyester materials. Chronic inflammation caused by foreign-body cell infiltration is thought to remain as a foreign-body granuloma, and foreign-body granulomas may themselves be a cornerstone of the embolic

site and may increase mechanical strength [16]. However, there is no previous research clarifying the significance of foreign-body reactions in coil embolization. The long-term usefulness of the fibered coil should be determined from further experimental studies and long-term clinical results in the future.

This study had some limitations. First, the number of subjects in each group was small. Second, we treated carotid arteries that were smaller in size than a vessel in VAA or peripheral vascular disease. However, it is technically difficult to create an aneurysm in an abdominal vessel, and we used the carotid artery as an alternative. In future research, it is necessary to consider whether the combination of fibered coil and bioactive coil improves physical fitness and leads to clinical outcome.

In conclusion, there are histopathological differences between experimental aneurysms treated with bare platinum coils, fibered coils and bioactive coils. Fibrosis was more prominent in aneurysms treated with bioactive coils, and foreign-body giant-cell infiltration was found in aneurysms treated with fibered coils. Although our results suggest that bioactive coils are useful for wound healing, several other factors are involved in clinical situations. Hence, it is also necessary to verify the significance of bioactive coils in peripheral disease and the foreign-body response induced by fibered coils using additional clinical data.

Declaration of interest

There is no conflict of interest in this study.

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