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Evaluation of Particulate Embolic Materials with MR Imaging, Scanning Electron Microscopy, and Phase-Contrast Microscopy

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PURPOSE: To analyze the properties and embolic effect of microfibrillar collagen (MFC), Gelfoam powder, and polyvinyl alcohol (PVA) materials that are used in embolization procedures in the head and neck. **METHODS:** The shape and surface of these embolic agents were examined with scanning electron microscopy and phase-contrast microscopy. The mean number of areas of T2-weighted high signal intensity was measured on MR images in a rat embolization model to estimate the embolic effect. **RESULTS:** By scanning electron microscopy and phase-contrast microscopy, MFC appears fibriform and has various sizes and an irregular surface. Gelfoam is of uniform size and has a smooth surface. PVA materials are granulated and have a rough surface. MFC is somewhat suspendable and its shape changes moderately after suspension. Gelfoam is very suspendable and its shape changes rapidly. PVA showed only mild swelling. The embolic effect of MFC was the lowest of the materials examined. Large PVA particles (250 to 500 μm) showed a lesser embolic effect than Gelfoam or small PVA particles (50 to 150 μm) or medium-sized PVA particles (150 to 250 μm). No significant differences were observed among the embolic effects of Gelfoam, small PVA particles (50 to 150 μm), and medium PVA particles (150 to 250 μm). **CONCLUSIONS:** MFC and large PVA particles (250 to 500 μm) should be used for embolization of vascular anatomy involving potentially dangerous anastomoses. Gelfoam, PVA particles of 150- to 250- μm diameter, and PVA particles of 50- to 150- μm diameter are adequate for embolization involving homogeneous and peripheral anatomy.

Index terms: Interventional materials, embolic agents; Interventional materials, polyvinyl alcohol foam

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Many embolic particulate agents have been used in head and neck embolization. The use of microfibrillar collagen (MFC), Gelfoam powder, and polyvinyl alcohol (PVA) is well documented.

MFC (Avitene, Avicon, Fort Worth, Tex) is a topical hemostatic agent prepared from purified bovine collagen that has been used to control capillary bleeding in various surgical applications (1). MFC was described as an embolic

agent in 1978 (2); however, recanalization occurs, and it is primarily used for preoperative embolization (3). Because of the presence of bovine collagen, MFC is potentially antigenic; however, animal and human studies have not demonstrated any significant antigenic effects (4).

Gelfoam (Upjohn; Kalamazoo, Mich) was used to control hemorrhage during surgical procedures in 1945 (5). Speakman (6) reported the intravascular use of Gelfoam in 1964 (6). It is available as a powder (with particles ranging from 40 to 60 μm in size) that can be placed in contrast material and injected through small-lumen catheters. In general, caution is advised when using Gelfoam in the external carotid artery because of its small size and the multiple anastomoses between the external carotid artery and the intracerebral circulation (7). It can deeply penetrate the tumor bed, causing tumoral hemorrhage (8).

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PVA is converted into a spongelike material by foaming agents and is hardened with formaldehyde (9). PVA particles have proved to be a useful embolic material, particularly when long-term occlusions are desirable (10). To obtain a more uniform size, we divided blended PVA particles into three size categories: 50 to 150 μm , 150 to 250 μm , and 250 to 500 μm . PVA has a high coefficient of friction that sometimes makes smooth injection difficult. Various maneuvers have been suggested to overcome this problem (11–13). The clinical efficiency of these embolic materials in therapeutic neuroradiology has been well described; however, the objective estimations of the embolic effect have been limited. We examined the shape and surface of the embolic materials by scanning electron microscopy and used phase-contrast microscopy to study the changes in the shape of these embolic agents in suspension. We also examined their embolic effect in rats by using magnetic resonance (MR) imaging.

Materials and Methods

The examined materials were MFC ($<1000\ \mu\text{m}$), Gelfoam powder (40 to 60 μm) and PVA. A blended mixture of PVA was divided into three size fractions: small (50 to 150 μm), medium (150 to 250 μm), and large (250 to 500 μm). Each particulate fraction was purified by using an exact sieve, and the size range of each fraction was confirmed with scanning electron microscopy.

Scanning Electron Microscopy and Phase-Contrast Microscopy

MFC, Gelfoam, and medium-sized PVA particles were examined. The dried specimens were coated with gold in a vacuum evaporator and subsequently examined with scanning electron microscopy ($\times 30$, $\times 300$, and $\times 1500$) (14).

Each material (10 mg) was suspended in 5 mL of contrast medium (Iopamiron-300, Nihon Schering KK; Osaka, Japan) and 5 mL of normal saline. The changes in each material that occurred during suspension were evaluated by using phase-contrast microscopy ($\times 10$ and $\times 25$).

Rat Embolization Model

Adult male Sprague-Dawley rats weighing 350 to 450 g were anesthetized with ketamine (40 mg/kg). The neck area was shaved and cleaned. Preoperatively, a suspension of 10 mg of embolic material in 5 mL of contrast medium (Iopamiron 300) and 5 mL of normal saline was prepared.

Under a surgical microscope, we exposed the right common carotid artery, the internal carotid artery, and the external carotid artery via an anterior cervical incision. Each artery was clamped with microclips. A modified microcatheter (distal internal diameter of 0.6 mm) was inserted into the common carotid artery distal to the clamp. After the microclip of the internal carotid artery was removed, a 0.5-mL volume of the embolic suspension was injected slowly into the right common carotid artery of the experimental animals, and a 0.5-mL mixture of Iopamidol and normal saline was infused into the right common artery of five control rats. Any major defect that was present after the arteriotomy was closed with a 10-0 microsuture. The proximal carotid clamp was released to achieve a first-pass effect exclusively into the internal carotid artery (15). The clamp (microclip) on the external carotid artery was removed, and the skin was closed with 3-0 nonabsorbable sutures.

Embolization was performed with each of the following five materials: microfibrillar collagen ($<1000\ \mu\text{m}$) in five rats, Gelfoam powder (40 to 60 μm) in six rats, small PVA particles (50 to 150 μm) in nine rats, medium PVA particles (150 to 250 μm) in seven rats, and large PVA particles (250 to 500 μm) in seven rats.

MR Examination

One day after injection, the rats were examined on a 4.7 T MR system. The animals, under pentobarbital anesthesia (40 mg/kg), were placed prone and T2-weighted (1500/50 [repetition time/echo time]) coronal images of the brain were obtained with a 2.5-mm section thickness at four anatomic levels using a 256×128 matrix. The T2 high-signal-intensity area was measured to evaluate infarction and ischemic brain edema in both hemispheres. The high-intensity area was measured by means of manual planimetry and was expressed as a percentage of the total brain area at that level. Data were expressed as the mean plus or minus standard deviation. Differences in the mean high-intensity area between the groups were determined by Scheff's test after one-way analysis of variance. A *P* value of less than .05 was considered significant.

Histologic Examination

After the MR studies were completed, the rat brains were removed, fixed in 10% formalin, processed, and embedded in paraffin. Brain sections 4 μm thick were obtained in the coronal plane at levels corresponding to those depicted on the MR images and stained with hematoxylin-eosin. The stained sections were observed under light microscopy. The vessels occluded by embolus and the presence or absence of infarction and ischemic edema were determined. The criterion for infarction was visualization of liquefactive necrosis. The area of infarction and ischemic edema was compared with the high-intensity area by means of MR imaging.

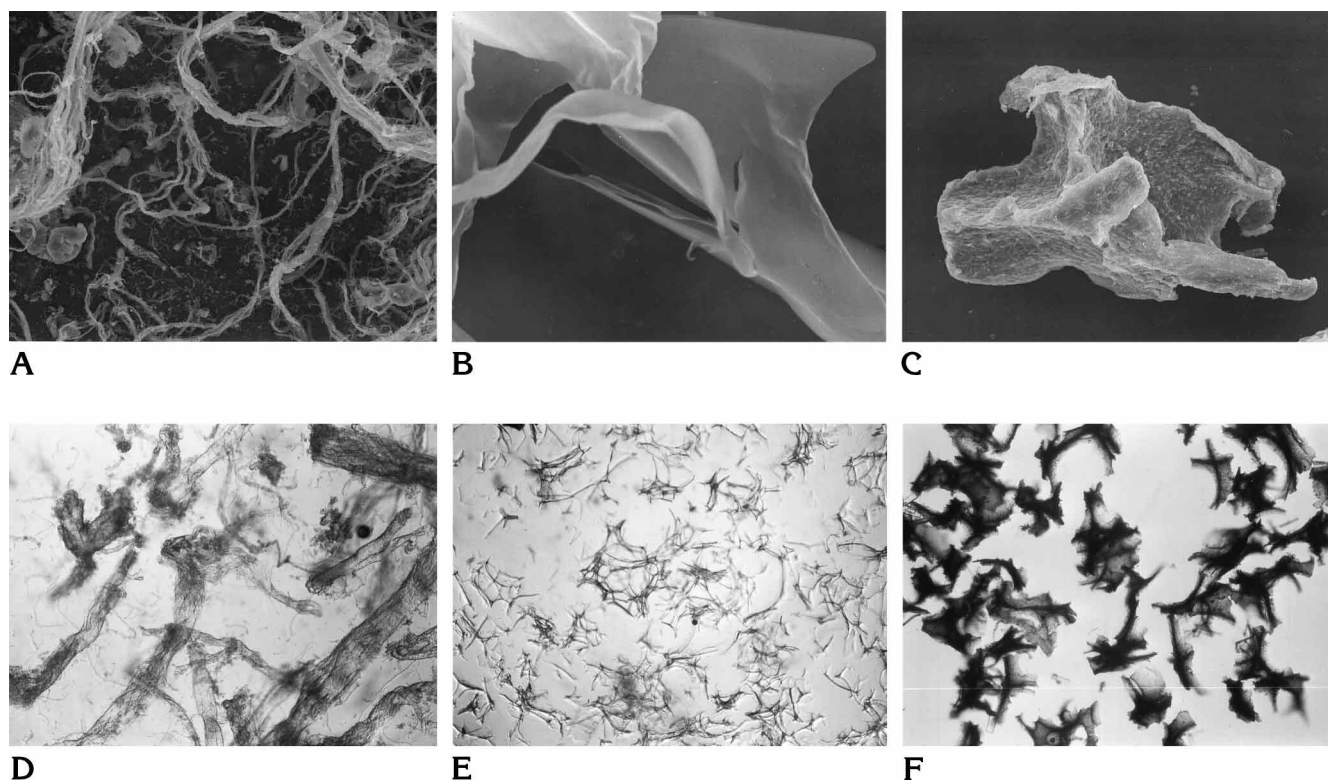


Fig 1. A–C, Scanning electron photomicrographs of microfibrillar collagen (A), Gelfoam powder (B), and PVA particles (150 to 250 μm) (C) (A, $\times 300$; B, $\times 1500$; C, $\times 300$).

D–F, Phase-contrast photomicrographs of microfibrillar collagen (D), Gelfoam powder (E), and PVA particles (150 to 250 μm) (F) ($\times 10$). Note changes in shape and surface of each embolic agent after soaking.

Results

Scanning Electron Microscopy and Phase-Contrast Microscopy (Fig 1)

By scanning electron microscopy, MFC appears fibrinous and irregular in size and has a rough surface. Gelfoam powder is of intermediate texture, and its surface is smooth. PVA is granulated and has a rough surface. By phase-contrast microscopy, MFC is suspendable and it enlarges moderately in suspension. Gelfoam powder is very suspendable, and the edges dissolve in normal saline and lopamidol. Extreme changes in its shape were noted. Suspensions of MFC and Gelfoam resemble a colloidal solution. PVA is less suspendable and expands mildly in suspension.

MR Imaging (Fig 2)

No significant differences were found among the groups of rats for any of the physiological variables measured, including arterial oxygen

pressure, partial pressure of carbon dioxide, hydrogenion concentration, blood pressure, heart rate, temperature, and serum glucose. Table 1 shows the rate of occurrence of high-intensity areas in the rat brain after injections of various embolic agents. No area of high signal intensity was observed in the five control animals.

Areas of high signal intensity were observed in the ipsilateral cerebral cortex in all five rats in the MFC embolization group. In the Gelfoam embolization group, diffuse areas of high intensity were seen throughout the entire hemisphere on the side operated on in three of the six rats, and the remaining three rats showed high-intensity areas in the cerebral hemispheres bilaterally. In the group in which embolization was done with small PVA particles, diffuse areas of high signal intensity were detected throughout the cerebral hemisphere on the embolized side in seven of the nine rats, and scattered areas of high intensity were seen in the cortex and/or basal ganglia on the embolized side in the remaining two rats. Diffuse areas of high signal

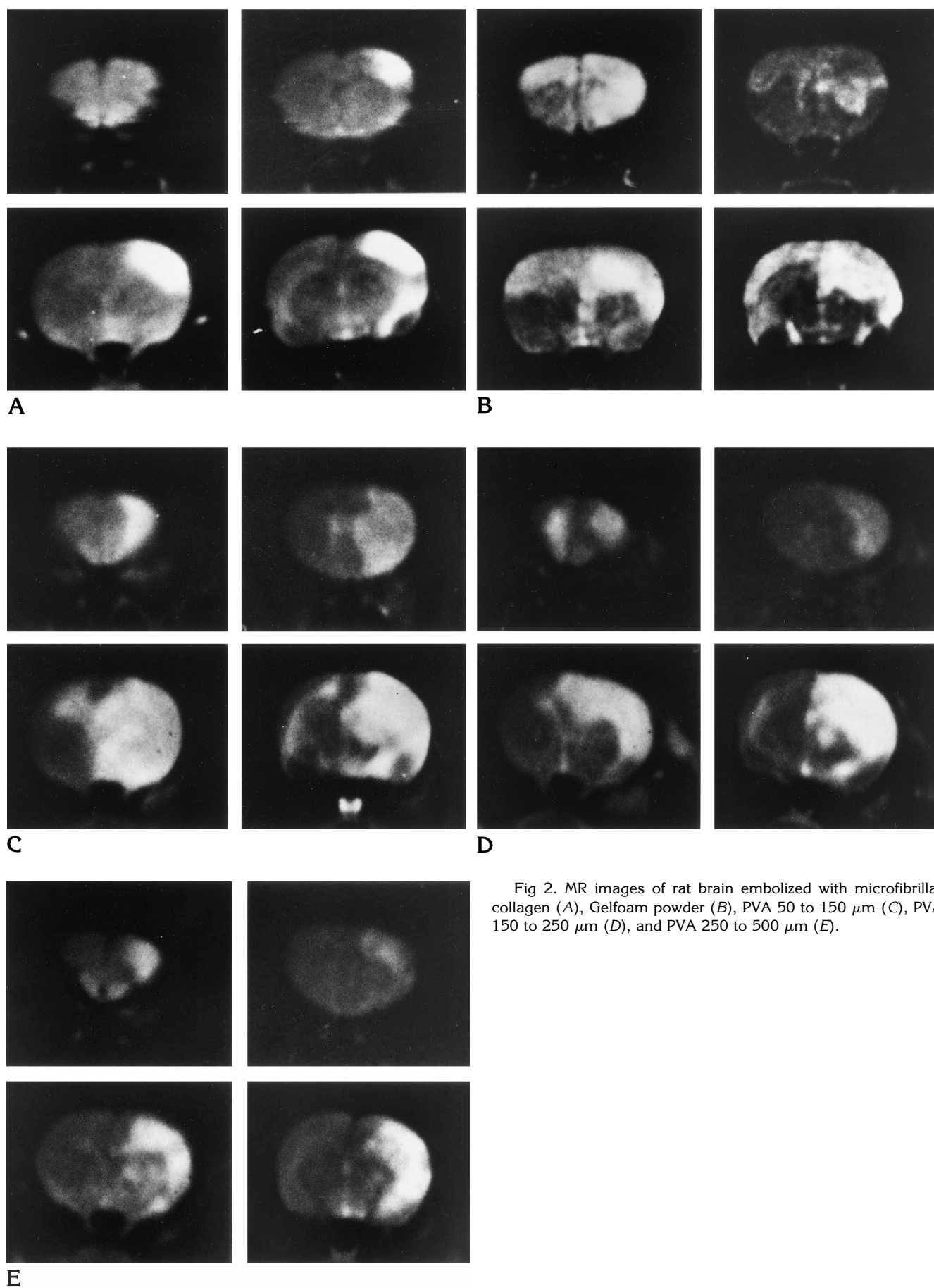


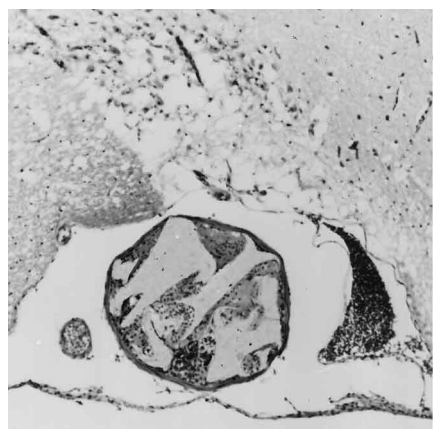
Fig 2. MR images of rat brain embolized with microfibrillar collagen (A), Gelfoam powder (B), PVA 50 to 150 μm (C), PVA 150 to 250 μm (D), and PVA 250 to 500 μm (E).

TABLE 1: Rate of occurrence of T2-weighted high-signal-intensity areas in the rat brain after embolization

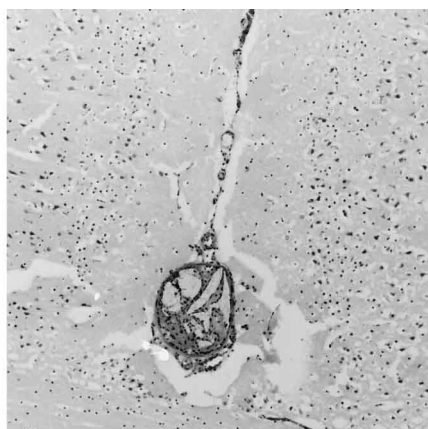
| Embolitic Material | No. of Animals | No. of Animals with Scattered Areas of High Signal Intensity in the Cortex and/or Basal Ganglia | No. of Animals with Diffuse Areas of High Signal Intensity in the Whole Hemisphere (Bilateral) |
|------------------------------|----------------|---|--|
| Microfibrillar collagen | 5 | 5 | 0 |
| Gelfoam powder | 6 | 0 | 6 (3) |
| PVA (50–150 μm) | 9 | 2 | 7 |
| PVA (150–250 μm) | 7 | 5 | 2 |
| PVA (250–500 μm) | 7 | 5 | 2 |

TABLE 2: Vessels occluded after injection of embolic materials

| Embolitic Material | No. of Animals | No. of Animals with Occluded Internal Carotid Artery | No. of Animals with Occluded Distal Middle Cerebral Artery and/or Anterior Cerebral Artery |
|------------------------------|----------------|--|--|
| Microfibrillar collagen | 5 | 5 | 0 |
| Gelfoam powder | 6 | 6 | 6 |
| PVA (50–150 μm) | 9 | 9 | 7 |
| PVA (150–250 μm) | 7 | 5 | 2 |
| PVA (250–500 μm) | 7 | 7 | 0 |



3



4

Fig 3. Photomicrograph shows PVA particles (250 to 500 μm) in the internal carotid artery (hematoxylin-eosin, original magnification $\times 30$).Fig 4. Photomicrograph of small leptomeningeal vessel shows PVA particles (50 to 150 μm) (hematoxylin-eosin, original magnification $\times 30$).

intensity were detected in the entire cerebral hemisphere on the embolized side in two of the seven rats in which large PVA particles were used, and scattered areas of high intensity were seen in the cortex and/or basal ganglia in the remaining five rats.

Histologic Examination

Histologic examination of the brain sections resected from the levels corresponding to MR images showed infarction and ischemic edema. Table 2 presents a summary of the vessels occluded after injection of the various embolic agents. MFC and large PVA particles occluded only the internal carotid artery on the embolic side (Fig 3). Gelfoam emboli were observed in the leptomeningeal arteries in all six rats in this

embolization group. Leptomeningeal arterial occlusion was also observed in seven rats in which small PVA particles were used and in two rats in which medium PVA particles were used (Fig 4). There was good correlation between the histologic areas of infarction and areas of high signal intensity (Fig 5).

The embolic effect of each material was evaluated as the percentage of high-signal areas seen on four sections of brain per rat (Fig 6). The mean percentage of areas of high signal intensity for each embolic agent was $4.72\% \pm 4.06\%$, $37.25\% \pm 14.67\%$, $41.54\% \pm 14.27\%$, $27.7\% \pm 11.59\%$, and $19.4\% \pm 11.8\%$ for MFC, Gelfoam, small PVA particles, medium PVA particles, and large PVA particles, respectively. The embolic effect of MFC was less than that of

Fig 5. Coronal section of rat brain embolized with microfibrillar collagen (A) and Gelfoam powder (B) (hematoxylin-eosin original magnification $\times 2.5$).

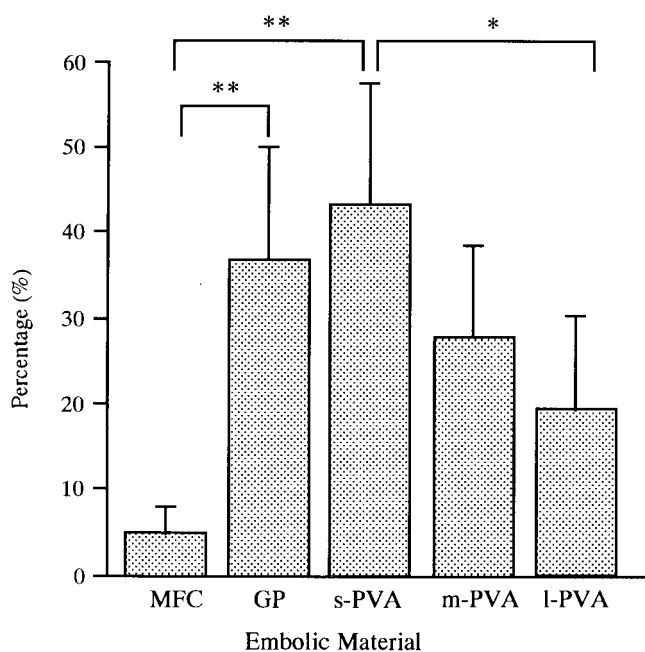
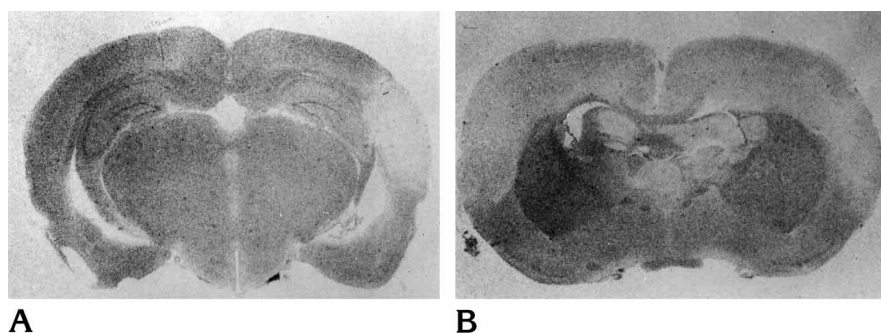


Fig 6. Bar graph shows mean T2 high-intensity area as a percentage of the area of the bilateral hemispheres. Values are given as mean plus or minus standard deviation. Single asterisk indicates $P < .05$; double asterisks, $P < .01$; MFC, microfibrillar collagen; GP, Gelfoam powder; s-PVA, small polyvinyl alcohol particles (50 to 150 μm); m-PVA, medium polyvinyl alcohol particles (150 to 250 μm); l-PVA, large polyvinyl alcohol particles (250 to 500 μm).

Gelfoam and small PVA particles ($P < .01$), and the effect of large PVA particles was less than that of small PVA particles ($P < .05$).

Discussion

MFC, Gelfoam, and PVA are commonly used embolic agents in procedures involving the head and neck. The choice of embolic agents depends on the objectives of the procedure, the selectivity desired, and the vascular anatomy of the pathologic territory. *Particulate embolization* refers to a mechanical blockage of vascular territory done with precut particles that may be

of uniform or variable size and shape. Their capacity to occlude is related to their size, shape, and coefficient of friction (7). We examined the surfaces of three embolic materials by using scanning electron microscopy and observed the changes in their shape during suspension by using phase-contrast microscopy. We also determined the embolic effect of these embolic agents in animal models.

Our observations with scanning electron microscopy suggest that MFC apparently acts as a large particle because of its rough surface and irregular size. Gelfoam is small and has a smooth surface, allowing it to penetrate deeply and occlude the capillary or precapillary vessels. Because PVA particles have a rough surface, the potential for penetration is decreased by their external irregularities. Furthermore, the results of phase-contrast microscopy indicate that MFC acts as a large particle, retaining its irregular shape after being soaked and becoming swollen. Gelfoam powder can penetrate deeply even in suspension, but PVA has little potential for penetration, retaining its rough surface even after soaking and swelling.

MFC has the least embolic effect cerebrally, followed by large particles of PVA. Previous reports indicate that MFC can penetrate arterioles as small as 100 μm in diameter (3). However, in our experiment, the concentration of the solution used was lower than that, and the injected volume was smaller. The suspension concentration may influence the embolic effect of each agent. Ischemic edema of the ipsilateral cortex developed in the rats in which MFC was used owing to the thrombotic effect or watershed type of occlusion from the proximally occluded internal carotid artery. The embolic effect of large particles of PVA seems to be due to the thrombotic effect from the proximally occluded vessels, because large PVA particles are too big to penetrate and occlude capillary or precapil-

lary vessels. Further experiments are needed to explain the difference in embolic effects between MFC and large PVA particles.

The cerebral embolic effects of Gelfoam and small PVA particles were greater than those of MFC. In particular, the animals in whom Gelfoam was used showed diffuse leptomeningeal arterial occlusion, bilateral cerebral infarction, and ischemic edema. These findings indicate very deep penetration of Gelfoam. The embolic effect of Gelfoam is related to its small size, smooth surface, and good affinity for the solvent. The embolic effects of small and medium PVA particles were similar to that of Gelfoam despite their rough surface and swollen shape after solution. The potential of PVA particles to promote thrombosis may increase the area of infarction and ischemic edema (16). The embolic effect of PVA is strongly affected by its particulate size range. Our results suggest that for particles smaller than 250 μm , size has more influence on embolic effect than does external texture of the particles; however, for particles larger than 250 μm , texture has the greater influence.

Our observations of the shape and surface of various particulate embolic agents with scanning electron microscopy and phase-contrast microscopy are effective in explaining the embolic effect as assessed with MR imaging in rat embolization models. MFC and large PVA particles are suitable for use when there is a risk of distant embolus, dangerous anastomosis, and a large-vessel tumoral bed. Gelfoam and small and medium PVA particles are better for embolization involving homogeneous and peripheral anatomy.

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