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Embolization with Cellulose Porous Beads, II: Clinical Trial

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PURPOSE: To evaluate the clinical applicability of cellulose porous beads (CPBs) as an embolic material for permanent vascular occlusion. **METHODS:** Embolization with CPBs was performed in 16 patients, six with meningioma of the sphenoid wing, two with meningioma of the falx, three with meningioma of the tentorium, two with dural arteriovenous fistula, one with paraganglioma, and two with spinal arteriovenous malformation. Surgical specimens were examined histologically. **RESULTS:** No complications were encountered in any of the 16 patients. Angiograms obtained after embolization showed satisfactory vascular stasis in all cases. Histologic examination of surgical specimens disclosed that vessels having approximately the same caliber as the CPB particles were occluded without stretching of the vessel wall. Larger vessels were occluded by aggregates of many particles, which left no open spaces. Although a few inflammatory cells were seen in the thrombosed vessels, inflammation evoked by CPB was mild and did not extend to either the vessel wall or to surrounding tissues. **CONCLUSION:** CPBs were easy to inject through microcatheters, traveled to distal sites, and produced homogeneous and peripheral embolization without inflammatory changes different from other embolic materials. CPBs are a good embolic material for permanent occlusion in the clinical setting.

Index terms: Arteries, therapeutic blockade; Interventional materials, particles and microspheres

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In a previous study, we investigated the properties, characteristics, and techniques of embolization with cellulose porous beads (CPBs, manufactured by Asahi-Kasei, Nobeoka, Japan) in dogs (1). This material has significant apparent engineering and mechanical advantages over the currently used polyvinyl alcohol (PVA) foam. The beads are uniform in size, have a specific gravity similar to blood, and are positively charged, resulting in an embolic material that is easy to use and efficient in vessel occlusion. In that experimental study, the CPB was used to occlude the unilateral renal circulation in 12 dogs. The effects were evaluated immediately, 1 hour, 4 weeks, and 12 weeks after embolization. There was no evidence of revascularization during the follow-up period. Histologically, the CPBs excited very little inflammatory reaction and the beads were distributed distally in the vessels with no open spaces. Here, we describe our preliminary clinical trial of CPB embolization. The study protocol was approved by the local ethical committee and informed consent was obtained from the patients or from their closest relatives.

Subjects and Methods

Sixteen patients underwent embolization with CPBs: six had meningioma of the sphenoid wing, two had meningioma of the falx, three had meningioma of the tentorium, two had dural arteriovenous fistulas (AVFs), one had a paraganglioma, and two had spinal arteriovenous malformations (AVMs). Ten patients were female and six were male, and they ranged in age from 13 to 66 years (mean age, 51 years). The Table summarizes the data on each patient. In the patients with dural AVF, platinum microcoils were used to obliterate the main trunk of the artery after CPB embolization.

CPBs of two sizes (150 and 200 μm diameter) were suspended in iodinated contrast material (about 2000

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Clinical details of 16 patients undergoing embolization with CPBs

Case	Age, y/Sex	Location and Lesion Type	Embolized Vessel	Particle Size, μm	Days before surgery
1	49/F	Sphenoid wing meningioma	MMA	200	5
2	55/F	Sphenoid wing meningioma	MMA	200	4
3	64/F	Sphenoid wing meningioma	MMA, STA	150, 200	3
4	52/F	Sphenoid wing meningioma	MMA, STA	200	5
5	59/M	Sphenoid wing meningioma	MMA	200	3
6	65/M	Sphenoid wing meningioma	MMA, STA	150, 200	8
7	13/F	Tentorial meningioma	STA	150, 200	2
8	64/F	Tentorial meningioma	MMA, OA, PAA	150, 200	3
9	48/M	Tentorial meningioma	MMA, OA	200	4
10	66/F	Falx meningioma	MMA	200	10
11	49/F	Falx meningioma	MMA, ACA	150, 200	4
12	60/F	Orbital paragnaglioma	OPA	150, 200	21
13	52/F	Dural AVF involving lateral sinus	OA, PAA, APA	200	. . .
14	39/M	Dural AVF involving lateral sinus	MMA, OA, PA	200	. . .
15	32/M	Spinal AVM	T-4 FSCBASA	200	. . .
16	41/M	Spinal AVM	T-8 FSCBASA	200	. . .

Note.—CPBs indicates cellulose porous beads; MMA, middle meningeal artery; STA, superficial temporal artery; OA, occipital artery; PAA, posterior auricular artery; ACA, anterior cerebral artery; OPA, ophthalmic artery; AVF, arteriovenous fistula; APA, ascending pharyngeal artery; AVM, arteriovenous malformation; TA, tentorial artery; and FSCBASA, feeder of sulcal commissural branch of the anterior spinal artery.

CPBs per 1 mL) and sterilized in vapor at 121°C at 11 Pa for 20 minutes; the quality of sterilization of each batch was bacteriologically tested. All procedures were performed in the interventional neuroangiography suite with high-resolution digital subtraction angiography with the road-mapping technique. Embolization was performed with the use of a local anesthetic by means of the transfemoral approach; the patients were awake throughout the procedure. A 6F sheath was placed into the femoral artery, and a 6F guiding catheter was inserted through the sheath. The patients received a bolus of 3000 units of heparin intravenously; supplemented with 1000 units of heparin as needed every hour. Heparinization was reversed with protamine sulfate at the end of the procedure. Most embolizations were performed with a Tracker-18 catheter (Target Therapeutics, Fremont, Calif). The tip of the microcatheter was gently guided into the proper artery and positioned precisely. After superselective angiography, each patient received an injection of an appropriate dose (usually 30 mg) of amobarbital. An immediate neurologic examination was performed to detect temporary neurologic deficits related to this injection. After confirming a negative amobarbital test, appropriately sized CPBs were infused slowly until complete obliteration was obtained under direct fluoroscopic view. The catheter was then withdrawn smoothly and a final angiogram was obtained to check the occlusion of the embolized arteries. Vital signs and neurologic function were monitored during and after the procedure.

Except for the two patients with dural AVFs and the two with spinal AVMs, embolization was followed by surgery. The time between embolization and surgery was 2 to 21 days. The surgical specimens, fixed in 10% neutral buffered formalin and routinely processed for light microscopy, were sectioned at 3 μm and stained both with hematoxylin-eosin and Giemsa stains.

Representative Cases

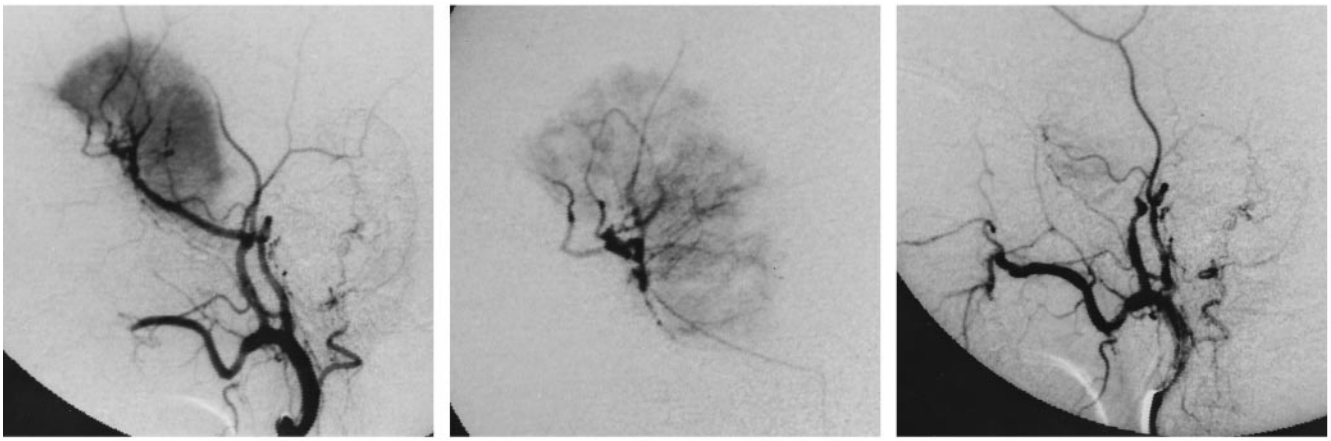
Case 1

A 55-year-old woman had a history of headache and blurred vision lasting a few months. On admission she was alert and well oriented. Cranial nerve function was intact except for papilledema of the optic fundi and disturbance of visual acuity and of the visual fields. Magnetic resonance (MR) imaging showed a large meningioma of the left sphenoid wing. The tumor was supplied mainly from the left middle meningeal artery. Via the transfemoral route, a Tracker-18 catheter was introduced into the artery. CPBs measuring 200 μm in a 3-mL suspension were infused slowly over a period of 5 to 10 minutes until the tumor stain was imperceptible under direct fluoroscopic view. An angiogram obtained immediately after the procedure showed complete obliteration of the middle meningeal artery (Fig 1A–C). After treatment, the patient showed no neurologic change. Four days later, the tumor was surgically removed with good hemostasis. The estimated surgical blood loss was 540 mL.

Microscopically, the embolized vessels were near the dural surface. CPBs reached vessels measuring approximately 200 μm in diameter. Larger vessels were occluded by aggregates of particles that left no open space. There was no disruption of the vessel wall and no evidence of perivascular hemorrhage. Many red blood cells and several white blood cells were found within the CPB aggregates. No inflammatory changes of the vessel wall or the surrounding tissues were seen (Fig 1D).

Case 2

A 13-year-old girl had a history of double vision lasting a few months. On admission she was alert and well oriented. Cranial nerve function was intact except for right



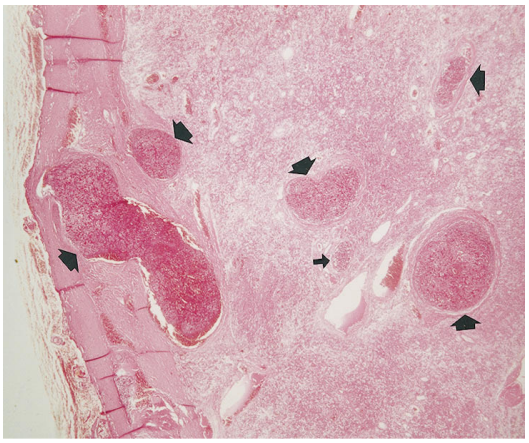


Fig 1. *A*, Left external carotid angiogram (lateral view) shows blood supply to a meningioma of the sphenoid wing via the middle meningeal artery.

B, Superselective angiogram shows a dense tumor stain.

C, After embolization, the middle meningeal artery is occluded just proximal to the tumor and no tumor stain is recognizable.

D, Photomicrograph of the surgical specimen shows CPBs reaching vessels measuring approximately 200 μm in diameter (*thin arrow*). Larger vessels near the dural surface are packed with numerous particles without gaps (*wide arrows*). There is no disruption of the vessel wall and no evidence of perivascular hemorrhage. CPBs are stained dark red (hematoxylin-eosin, original magnification $\times$20).

trochlear nerve palsy. MR imaging showed a right tentorial meningioma. The tumor was supplied mainly from the right tentorial artery. Via a transfemoral route, a Tracker-18 catheter was introduced into the right tentorial artery. CPBs measuring 150 μm in a 6-mL suspension were injected first, followed by 200-μm CPBs in a 2-mL suspension to achieve a more proximal occlusion. An angiogram obtained immediately after the procedure showed complete obliteration of the tentorial artery (Fig 2A–C). After treatment, the patient showed no neurologic change. Two days after embolization, the tumor was removed surgically with good hemostasis. The estimated surgical blood loss was 460 mL.

Microscopically, CPBs of 150 and 200 μm reached vessels of approximately the same size. A larger vessel was occluded tightly by aggregates of particles of both sizes without any open spaces. There was no disruption of the vessel wall and no evidence of perivascular hemorrhage. Several old red and white blood cells were found within the CPB aggregations (Fig 2D).

Case 3

A 32-year-old man had a history of slowly progressive paresthesia and weakness of the lower limbs. Examination revealed lower-extremity paraparesis, absent rectal tone, and paresthesia below the midthoracic level. A spinal angiogram showed a large nidus-type AVM located at the T-5 and T-6 levels. It was fed by the radiculomedullary artery arising at the right T-4 intercostal artery. Via the transfemoral route, a Tracker-18 catheter was advanced to the appropriate position within the sulcal commissural branch of the anterior spinal artery leading toward the AVM. CPBs measuring 200 μm in a 12-mL suspension were infused slowly over 15 minutes. An angiogram obtained immediately after the procedure showed almost complete disappearance of the AVM with preservation of the anterior spinal artery. After treatment, the patient showed clinical improvement. A repeat arteriogram obtained 1 year later disclosed no evidence of recanalization, and angiograms of the other adjacent pedicles also showed absence of an AVM nidus (Fig 3).

Results

Satisfactory and technically easy and safe embolizations were achieved in all 16 patients. Using CPB, we were able to perform superselective embolization of the feeding arteries

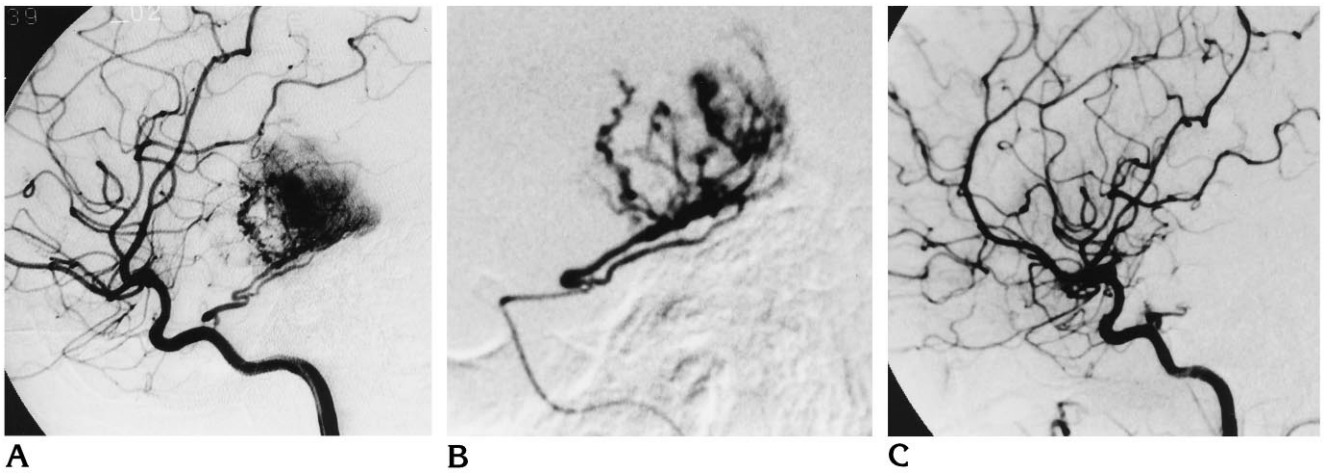
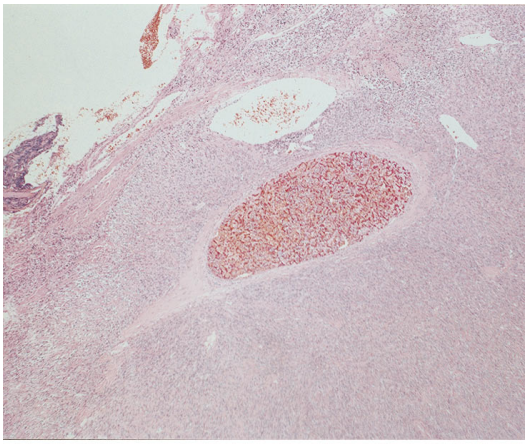


Fig 2. *A*, Right internal carotid angiogram (lateral view) shows blood supply to a tentorial meningioma via the medial tentorial artery.

B, A superselective angiogram of the medial tentorial artery (lateral view) shows a tumor stain.

C, After embolization, no tumor stain is visible on the internal carotid arteriogram.

D, Photomicrograph of the surgical specimen shows a large vessel packed densely with several CPBs without gaps. There is no disruption of the vessel wall and no evidence of perivascular hemorrhage. CPBs are stained dark red (hematoxylin-eosin, original magnification ×20).



through a microcatheter. No apparent skin or muscle necrosis occurred, nor were neurologic or pulmonary complications encountered during or after the procedure in any of the patients. Good hemostasis was obtained in patients who subsequently underwent surgery.

Angiographically, satisfactory stasis was noted in the immediate phases after embolization. CPBs produced a rapid and drastic reduction in blood flow.

Microscopically, CPBs measuring 150 and 200 μm in diameter reached vessels at the tumor surface that were approximately 150 and 200 μm in diameter. Larger vessels were occluded by aggregates of particles that formed a dense thrombus without open spaces. There was no disruption of the vessel wall and no evidence of perivascular hemorrhage. Few inflammatory cells were seen in the thrombosed vessels and inflammation evoked by the CPB was mild and did not extend to either the vessel wall or the surrounding tissues.

Discussion

Particle embolization refers to mechanical blockage of a vascular territory by means of precut particles that may be of uniform or variable size and shape. Their ability to occlude is related to their size, shape, and coefficient of friction.

Different materials of the nonabsorbable particulate type have been tested for their ability to provide permanent occlusion. PVA foam is probably the most commonly used and is considered an ideal particulate embolic agent for vascular occlusion. PVA started out in block form, and shavings of various sizes can be prepared for clinical use (2–5). The particles are absorbed slowly and expand to occlude arteries larger than the internal diameter of the delivery catheter. They produce an inflammatory reaction characterized by polymorphonuclear leukocyte infiltration in the wall of the embolized artery at 2 weeks after introduction (6). These

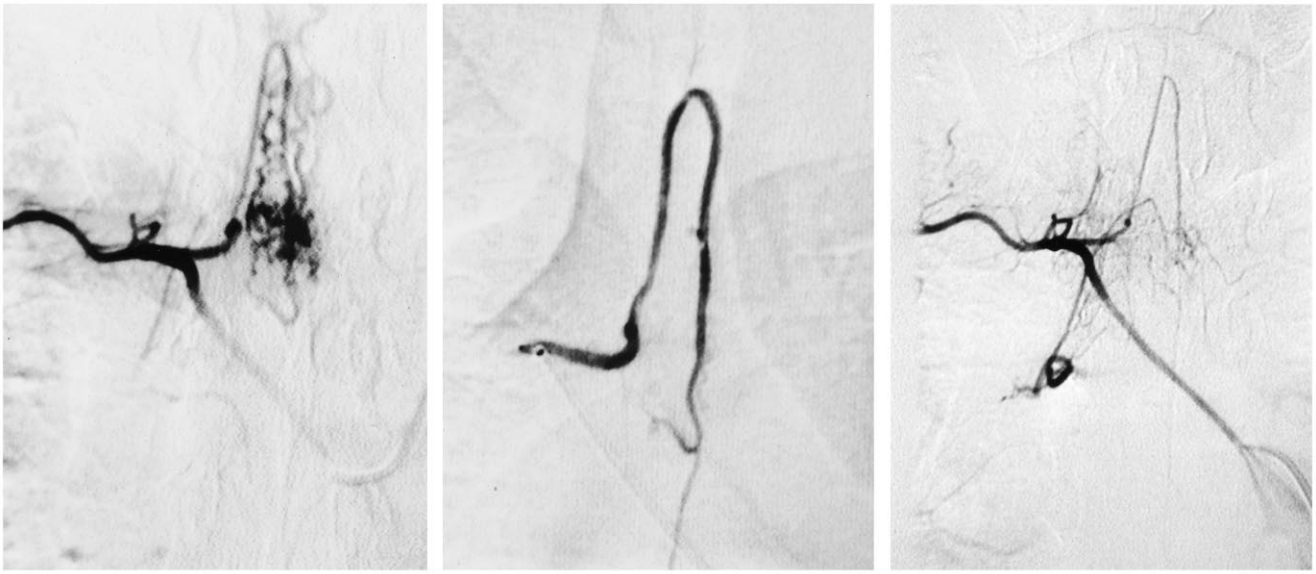


Fig 3. *A*, Selective angiogram of a radiculomedullary artery arising from the right T-4 intercostal artery shows an intramedullary glomus-type arteriovenous malformation (AVM).

B, An angiogram obtained immediately after the embolization procedure shows complete occlusion of the AVM.

C, A repeat angiogram obtained 1 year after embolization shows no evidence of recanalization.

inflammatory changes subsequently disappear and are replaced by a giant-cell foreign-body reaction by 3 months; an adherent, organized, partially calcified thrombus containing PVA is found at 9 months (3, 7). It has been suggested that PVA serves as a matrix for fibroblasts, accounting for its relative permanence (3, 7, 8). However, the resulting vascular occlusion may not be permanent, since recanalization can occur around the particles.

Dextran microspheres (Sephadex; Pharmacia, Uppsala, Sweden) have been used in experimental partial splenic embolization procedures (9). This material was found to be superior to PVA and silicone because the microspheres remained in suspension longer, did not clump or shatter, and produced a more homogeneous and peripheral embolization. Dion et al (10) further analyzed the properties of dextran microspheres both in vitro and in vivo, and reported their clinical experience. They also found dextran microspheres to be superior to earlier materials because of their ease of use and injection and their greater control resulting from their isogravitational suspension and decreased friction, which reduced the possibility of their clogging the microcatheter. Because of their specific gravity (1.1*g*), small size, and smooth, round surface characteristics, these microspheres reached more distal sites and produced more complete and permanent occlusions. They did not incite the inflammatory vessel wall component associated, for example, with PVA. However, these particles were not uniform in size; Sephadex G-25 is 40 to 150 μm in diameter and Sephadex G-50 is 100 to 300 μm in diameter (9–11). In some experimental cases, there was disruption of the vessel wall caused by the swelling of particles, which approximately doubled in size at their final destination in the vessel.

Flandroy et al (12) evaluated (D, L) polyactide microspheres, which have a spherical, smooth shape and come in an accurately calibrated range of sizes. Spherical particles can travel more distally than irregularly shaped ones and can produce homogeneous and complete occlusion. The size distribution curve revealed very little granulometric dispersion. These investigators confirmed that PVA particles of approximately the same size as the PVA microspheres agglomerated more proximally owing to their irregular and sharp-edged shapes. Sometimes they agglomerated in the delivery system itself. Variations in particle size may result in complications. Precise calibration of spherical particles is important in procedures involving the spinal cord in order to exclude smaller particles that can occlude the spinal artery.

Beaujeux et al (13) conducted a clinical evaluation of trisacryl gelatin microspheres with 105 patients who had tumors or facial, spinal cord, or cerebral AVMs. The microspheres they used had been shown to have biocompatibility in a previous study with animals (14). This material is precisely calibrated, perfectly spherical, and soft but nonresorbable, and thus can be used for embolization. It was possible to control the embolization by precise accounting of the amount of microspheres and by matching the particle size to the size of the pathologic vascular network.

CPBs remained in suspension for prolonged periods without clumping, because they are positively charged particles that repel one other, and their specific gravity is similar to that of whole blood. We found that because of their exceptionally uniform size, CPBs could be smoothly injected without clogging the microcatheter.

In all our patients, satisfactory stasis was shown on angiograms obtained in the immediate phase after embolization. CPB sometimes produced a rapid and drastic reduction in blood flow. Therefore, great caution must be exercised to avoid overembolization and reflux. Appropriate embolization can be achieved by gentle injection with a small syringe and careful fluoroscopic monitoring of the slowing of the blood flow.

Examination of surgical specimens disclosed that vessels with approximately the same caliber as the CPB particles were occluded without stretching of the vessel wall, a feature that was attributed to the fact that CPBs have a specific gravity similar to whole blood and are exceptionally uniform in size. Larger vessels were occluded by aggregations of particles that formed a dense thrombus without any gaps. This configuration is extremely important for achieving permanent occlusion, because recanalization occasionally occurs if there are open spaces between the particles. Although a few inflammatory cells were seen in the thrombosed vessels, any inflammation evoked by the CPB was mild and did not extend to either the vessel wall or the surrounding tissues.

Our clinical results are consistent with those we obtained in our experimental study. To draw firm conclusions regarding the safety and efficacy of CPB embolization in the clinical setting, studies with large patient populations and long follow-up periods are needed. If the results of such studies continue to be encouraging, CPBs of various sizes will be developed for the embolization of dural AVFs and of cerebral and spinal AVMs.

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