Hydroxyapatite Ceramics As a Particulate Embolic Material: Report of the Clinical Experience

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BACKGROUND AND PURPOSE: Our newly developed biocompatible embolic materials, hydroxyapatite ceramic microparticles, have good visibility during injection control and were shown to be capable of producing effective occlusion of the distal arteriocapillary bed in an experimental animal study. The purpose of this present study was to evaluate hydroxyapatite ceramic microparticles for use in human meningioma embolization.

METHODS: Thirteen patients with meningiomas underwent preoperative superselective embolization with the use of hydroxyapatite microparticles. Radiologic and histopathologic studies of the surgical specimens were performed.

RESULTS: During embolization, no microcatheter clogging was observed and angiographic devascularization was consistently obtained without unexpected proximal occlusions. Histopathologic findings showed that there was mild inflammatory response in the thrombosed lumen.

CONCLUSION: Hydroxyapatite microparticles are excellent embolic materials for the treatment of human meningioma. They have excellent biocompatibility and good injection control, which produces occlusion of the distal arteriocapillary bed.

Preoperative embolization of meningiomas was initially reported by Manelfe et al in 1973 (1) and has come to be a widely recognized preoperative procedure aimed at devascularization and obliteration of the arteriocapillary beds (2–5). In our preliminary study, we evaluated the characteristics and embolic properties of hydroxyapatite microparticles, both angiographically and histopathologically, in experimental animal embolization. Hydroxyapatite microparticles proved to be an effective and safe embolic material. The present clinical study was undertaken to evaluate these hydroxyapatite microparticles, both angiographically and histopathologically, in patients with meningiomas.

Methods
All the procedures were performed after approval of the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University and after informed consent was obtained from the patients and/or their next of kin. Thirteen patients (six female, seven male; mean age, 56.5 years; age range, 35–73 years) with meningiomas at various locations (convexity, n = 6; sphenoid ridge, n = 3; parasagittal, n = 3; falx, n = 1) were enrolled in our study. Pre-embolization MR imaging and superselective cerebral angiography were performed for all patients. Hydroxyapatite microparticles (produced at 800°C), ranging between 100 and 250 μm in diameter, were sterilized by ethylene oxide gas during 24 hr before use. The suspension of hydroxyapatite was made in concentration, with 10 mg for 10 mL of 80% contrast media before injection. Microcatheters with transparent hubs were selected so that injection control of embolic materials could be visually monitored to prevent clogging of microcatheters. The transfemoral approach was used in all patients along with heparinization and local anesthesia. Diagnostic superselective angiography was performed immediately before embolization. Embolization was performed only in external carotid system feeders for preoperative purposes, and it was not performed in internal carotid artery feeders. After superselective catheterization of external carotid artery feeders, provocative testing with lidocaine and thiopental sodium was performed to check whether these arteries supplied any cranial nerves anastomosed to the ophthalmic arteries or cerebral arteries. Embolization was performed manually under fluoroscopic monitoring only for feeders that had negative results of provocative testing. Injection was discontinued when stagnation of flow was encountered.

After embolization, devascularization effect in each feeder was classified into two groups: group A (95%–100%) and group B (<95%). Patency of cannulated feeding arteries was checked angiographically immediately after embolization to...
detect proximal feeding arterial occlusion due to particle aggregation. Evaluation was performed by two neurosurgeons who were blinded to this study. In several feeders with positive results of the provocative testing, we used microcoils to obtain proximal occlusion; these vessels were not included in this study. The interval between embolization and surgery varied from 2 to 22 days (mean, 7.3 days). All the patients underwent surgery while under general anesthesia. After total or subtotal tumor removal, the sections of surgical specimens were examined with hematoxylin and eosin staining after incomplete decalcification.

**Results**

Embolization with hydroxyapatite microparticles was successfully performed in all 13 cases, for a total of 27 feeding arteries in meningiomas in various locations with no resulting general, focal, or neurologic complications. We experienced no microcatheter clogging during the embolization procedures. Microparticle injection was consistently easy. Control of injection was excellent because of the good visibility of the embolic agent, especially at the level of microcatheter hub. Tumor vascularity during the arterial to capillary phase was consistently noted to gradually decrease and finally disappear in all cases, so that tumor stain was not present during the venous phase. The devascularization grade of the vessels treated was A in all cases (Table). Unexpected feeder occlusion did not occur in any cases, and all the feeders were patent immediately after embolization, consistent with effective delivery of particles to the tumor arteriocapillary beds.

All 13 patients underwent total or subtotal tumor surgical removal. Histologic evaluation of incompletely decalcified specimens disclosed mild inflammatory response and lymphocytic infiltration in the vessels treated was A in all cases (Table). Unexpected feeder occlusion did not occur in any cases, and all the feeders were patent immediately after embolization, consistent with effective delivery of particles to the tumor arteriocapillary beds.

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perivascular spaces (Fig 1). No hemorrhage or angio-
necrosis was found in any of the specimens.

Discussion
Radiologic evidence of diffuse embolization con-
ists of two findings: the first is complete devascular-
ization of the tumor on angiograms, and the second
is complete patency of the feeders immediately af-
ter devascularization of the tumor, consistent with oblit-
eration of the distal arteriocapillary bed without un-
expected proximal occlusion of feeders. From this
standpoint, our material showed satisfactory results
(Fig 2A and B). Recent advancements in microcath-
eter and microwire technology and digital subtraction
angiography enabled us to perform tumor emboliza-
tion much easier and safer than before. Appropriate
selection of the cases, provocative testing before em-
bolization, and careful use of embolic agents have
also helped to reduce complications. However, sev-
eral reports of recanalization after embolization have
been published (4, 6), as have reports of complica-
tions of unclear cause, some of which may be related
to the characteristics of the embolic materials them-
elves (6–8), such as intratumoral or peritumoral
hemorrhage around the occluded vessels (9–11),
edema around the occluded vessels (10), and AVF.

An advanced inflammatory response is considered
to cause arterial necrosis and hemorrhage. Subcuta-
neous tissue implantation is said to be more sensitive
for detecting inflammation reaction to embolic ma-
terials than implantation in other organs, especially
the brain (12–14). Misiek et al (15) showed a very mild
inflammatory response with hydroxyapatite particles
in subcutaneous tissue, but polyvinyl alcohol particles
caus ed extensive fibrosis in subcutaneous tissue (16).
In this regard, hydroxyapatite produces milder in-
flammation than does polyvinyl alcohol particles. On
the other hand, early recanalization sometimes results
from much less or almost no inflammatory response.

We experienced no hemorrhage or recanalization
during a follow-up period of ≥24 weeks after embo-
lization with our particles in our preliminary animal
study. In the histopathologic section of resected me-
ningiomas, hemorrhage and angionecrosis were not
shown and expected mild inflammatory signs were
shown, as were those of our animal experimental
study. The ideal benign inflammation reaction may be
obtained with hydroxyapatite particles.

More recently, it has been suggested that hydroxy-
apatite ceramics in a porous configuration be used as
a drug or antibody release system, which is another
unique characteristic of hydroxyapatite (7). These mi-
croparticles may even have a potential use as chemo-
therapeutic embolic material in the future.

Conclusion
In conclusion, hydroxyapatite ceramic micropar-
ticles constitute an excellent biocompatible embolic
material with good visibility during injection control.
They are capable of producing effective occlusion of
distal arteriocapillary beds, with a resulting mild be-
ign inflammatory response and preservation of the
arterial feeders.

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906