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A New Liquid Embolic Material, a 2-Hydroxyethyl Methacrylate-co-Methyl Methacrylate：a Safty Study in a Swine Endovascular Embolization Model

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Abstract：To study the safety, efficacy, and histopathology of a 2-hydroxyethyl methacrylate-co-methyl methacrylate (HEMA-co-MMA) embolic mixture in an animal model, microembolization of the rete mirabile was done in 13 swine. The consequences of super-selective injection of the two principal embolic mixture components (HEMA-co-MMA and 10% ethyl alcohol)were evaluated. Necropsy and histologic preparations were analyzed for pathology. The safety and efficacy of the material were confirmed. HEMA-co-MMA did not adhere to the catheter or cause vasospasm. Histopathologic examination of animals treated with HEMA-co-MMA revealed a mild inflammatory reaction around blood vessels and endothelial denuding in the acute and subacute stages. HEMA-co-MMA crystallized in the vessels within 2 weeks of injection. Crystals persisted without an inflammatory reaction for 3 to 6 months and had poor organization. Vessel walls became thin with disrupted internal elastic lamina and developed fibrosis after 3 to 6 months. HEMA-co-MMA is safe and effective, and does not cause any problems such as angitis, cytotoxic effect and recanalization.

Key words：**Angiography, Endovascular embolization model, HEMA-co-MMA, Histopathology, Liquid embolic material**

Introduction

Treatments for cerebral arteriovenous malformation (AVM) include the surgical extraction, endovascular embolization, and radiotherapy. Surgical extraction has been regarded as the best option, but its safety depends on the location of the AVM, the size of the lesion, and the clinical symptoms. Radiotherapy has become more popular recently, especially the gamma knife method, but this method also has its limits. Progress in development of digital subtraction angiography (DSA), microcatheters, and allied items, has enabled endovascular embolization to become an important supporting method for curative surgical extraction and radiotherapy.[1)]

Embolic materials used in endovascular embolization include liquids and solids, but because the liquids can block peripheral blood vessels better than the solids and can close the nidus itself, liquids are preferred. However, there is limited information about the technical efficacy of the liquids, angitis, and poisoning of nerve cells caused by the organic solvent, and recanalization due to liquefaction of liquid embolic materials.[2)-4)]

We developed, as a liquid embolic material, a polymer solution of HEMA-co-MMA. It is a copolymer of hydrophilic hydroxyethyl methacrylate (HEMA) and hydrophobic methyl methacrylate

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(MMA) and is made in a low concentration of ethyl alcohol and the contrast medium lopamidol.[5)–6)] We chose the rete mirabile (RMB) as a model for AVM. The RMB is well developed in cats, sheep, cows, pigs and a normal anatomical structure in these animals. The RMB is a network of blood vessels between the intracranial epidural part of the internal carotid artery and the external carotid artery and is used widely as a model of AVM in humans.[7)–11)] However, rete mirabile is different from cerebral AVMs in human, because of the lack of draining veins. We tested the feasibility of HEMA–co–MMA as embolic material in the RMB of swine.

Materials and Methods

1) Animals

Thirteen male swine (aged 5–17 months, average age 6.6 months. weight 18–55 kg, average weight 33.2 kg. Crown Mini, forwarded by Kagoshima Japan Form Co. Ltd) were divided into two groups. Group A received HEMA–co–MMA (n＝9), and group B received solvent only (n＝4).

2) HEMA–co–MMA preparation

Polymerization conditions are shown in Table 1. To exclude the monomer and other impurities from the polymer formed by radical polymerization in the presence of azo–bis–isobutyronitrile in the solvent, we dissolved the polymer with ethyl alcohol and precipitated it into water 3 times. Two solution of the purified polymer were prepared as described in Table 2. After dissolving HEMA–co–MMA in lopamilon 300, 99% ethyl alcohol, and physiological saline, the solutions were placed in amples and sterilized for 20 minutes in an autoclave at 121℃.[5)] A 10% ethyl alcohol solution was used as a vehicle control. With mixture of HEMA–co–MMA, the consistency of the material depends on the mixture ratio of these two materials.

3) Forming an embolism

After sedating the animal with ketamine (10 mg/kg), azaperon (2 mg/kg), and atropine sulfate (1 mg), we applied general anesthesia with 3% halothane, nitrous oxide, or intravenous thiopental sodium and began artificial ventilation. The presence of an RMB was confirmed by scanning the aorta and the common carotid artery by DSA(Figure 1A). We used a 4F main catheter or a microcatheter and the Seldinger method for DSA. After advancing a catheter through the selected side of the common carotid artery and the ascending pharyngeal artery, we placed the catheter in the proximal part of the RMB. We had slowly injected the HEMA–co–MMA into Group A animals, and the moment we could confirm back flow in the ascending pharyngeal artery, we stopped. This procedure was repeated 2 to 6 times. We discontinued the injections of HEMA–co–MMA when we confirmed the complete closing of the RMB (Figure 1B). The total amount of solution injected was 0.2 to 0.8 ml (average 0.4 ml). DSA was repeated 2 and 22 weeks after the injection to check for recanalization of the RMB. HEMA–co–MMA was in-

Table 1. Preparation of the polymer HEMA–co–MMA

HEMA (ml)	MMA (ml)	BenzOH (ml)	EtOH (ml)	AIBN (g)	Polymerization temp	Polymerization time
90	10	50	50	0.2	60°	47 min

HEMA：2－hydroxyethyl methacrylate, MMA：methyl methacrylate, BenzOH：Benzyl alcohol used as chain transfer agent, EtOH：Ethyl alcohol used as a solvent, AIBN：azo–bis–isobutyronitrile.

Table 2. Composition of embolic solutions

Solution code	HEMA–co–MMA (g)	Iopamilon 300 (ml)	EtOH (ml)	Saline (ml)
L	5	50	10	40
M	7.5	50	10	40

Iopamilon 300：Iopamidol 612.4 mg/ml, EtOH：Ethyl alcohol used as a solvent

jected on the opposite side of the RMB if necessary. In 1 animal, injection was done on both sides of the RMB at the same time.

The same procedures were used with Group B animals, but we injected 1 ml of 10% ethyl alcohol to one side of the RMB in 5 or 15 seconds, and after 4 to 7 days, we repeated the injection on the other side of the RMB.

4) Extraction of the RMB

We cut to open both common carotid arteries and let them bleed. We then did a craniotomy, and after extracting the brain, we extracted the RMB from the area of the cavernous sinus at the skull base (Figure 1C).

5) Pathology specimens

Each part of the extracted RMB was divided into 3 equal parts and fixed in 10% formalin plus 1% glutaraldehyde or frozen. Specimens were stained 4 ways and examined with a light microscope.

(1) Hematoxylin-Eosin stain

We cut the frozen specimens into slices 5 μm thick. To prevent the dissolution of the HEMA-co-MMA, we used isopropyl alcohol for dehydration.

(2) Elastica van Gieson stain

Formalin-fixed specimens were stained with Weigert's Resorcin-Fuchsin stain (Resorcin-Fuchsin 1A294, 0.1 g, 2% hydrochloric acid, 70% alcohol, 100 ml, CHROMA, Muensler, Germany) and Van Gieson contrast stain (saturated solution of picric acid, 100 ml, 1% acid Fuchsin solution, 5 ml).

(3) Basic Fuchsin-methylene blue stain

After the prefixation with 1% glutaraldehyde, we post-fixed with 1% O_sO_4 and embedded the tissue in a synthetic resin (Spur resin kit, TAAB, Berks, England). Slice 1 to 2 μm thick were made. After we stained the slice with methylene blue (pH 7 to 8 in 2% cacodylate buffer solution), while heating it on a hot plate, we rinsed it in distilled water and stained it with basic Fuchsin (1%

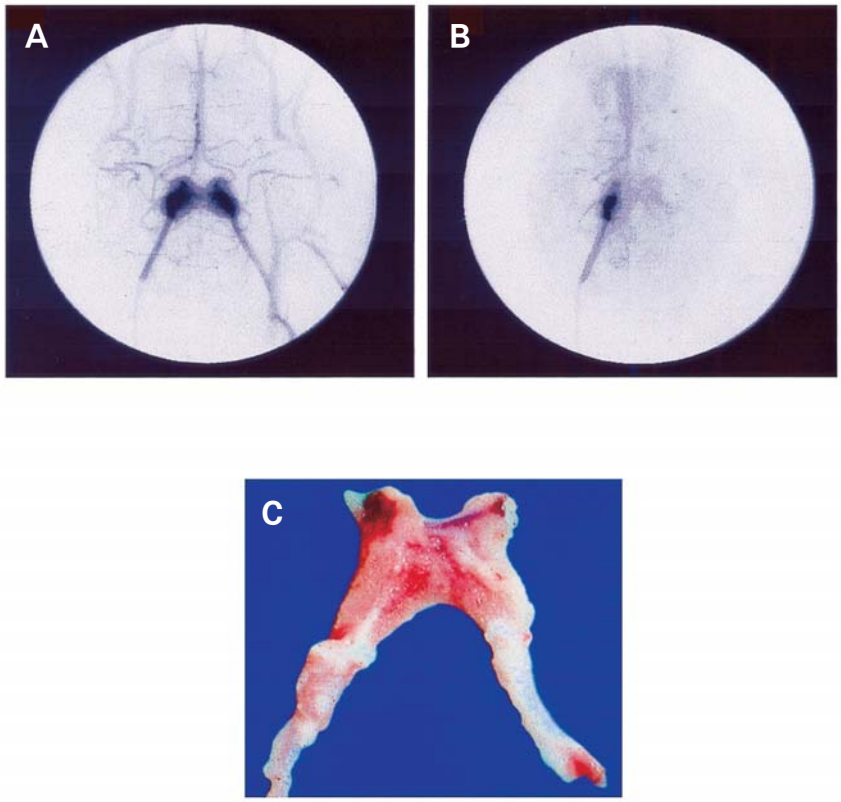

Figure 1. A : Angiography of the right common carotid artery (A-P view, before embolization) Both sides of the rete mirabile are contrasted. B : (A-P view, after embolization) Complete angiostenosis of the left rete mirabile is present. C : An extracted rete mirabile (A-P view)

solution in distilled water), at 80℃.

⑷ Immunohistochemical stain with von Willebrand factor

After deparaffined, the slice was treated with 0.01% protease by the labelled streptavidin biotin method. The first antibody, monoclonal mouse anti-human von Willebrand factor (DAKO, Glostrup, Denmark), was diluted 200 fold times and allowed to react for 20 minutes. The second antibody, biotinylated anti-mouse IgG (VECTOR, Burlingame, USA), was diluted 200 fold times and allowed to react for 30 minutes. The third antibody, alkaline phosphatase-conjugated streptavidin (DAKO, Glostrup, Denmark), was diluted 100 fold times and allowed to react for 30 minutes. We used the new Fuchsin method for color development.

Results

1) Endovascular embolization

⑴ Group A (HEMA-co-MMA, 18 RMBs)

All 18 RMBs were injected. A spasm of the ascending pharyngeal artery occurred after the endovascular embolization due to problem with the catheter. The injection volume was 0.2 to 0.8 ml (average 0.4 ml). Complete obstruction was achieved (Figure 1B). After the endovascular embolization, the catheter was easily removed because it was not adhered to the injected HEMA-co-MMA. It was possible to repeatedly perform the endovascular embolization with the same catheter. Neither of the solutions shown in Table 2 flowed into peripheral blood vessels. There were no technical problems with the solution.

⑵ Group B (Solvent solution, 8 RMBs)

Trouble with catheter manipulation in 2 of the RMBs had caused angiospasms in the ascending pharyngeal artery, and a thrombus occurred in 1 RMB that required termination of the test. Five RMBs were injected successfully. No angiospasms occurred in these 5 cases.

2) Recanalization of RMBs

In Group A, 2 weeks or 22 weeks after the first embolic procedure, we performed a second endovascular embolization on the opposite side of the RMB. In all 7 cases, there was no recanalization the complete obstruction of the RMB was confirmed. No vessel obstruction or angiospasm was seen in the proximal or distal arteries (Table 3).

Table 3. Summary of angiograhy and histopathology findings in Group A

RMB Sample Number	Recanalization (follow up)	follow-up	Angitis	Disruption of Elastica	Arterial wall atrophy	FBGC	Intimal hyperplasia	Angio-necrosis
1L	10Ws	3Ms	−	+++	+++	−	−	−
1R	NA	2Ws	−	+	+	−	+	−
2L	10Ws	3Ms	−	+++	+++	−	−	−
2R	NA	2Ws	−	+	+	−	+	−
3L	NA	2Ds	−	−	−	−	+	−
3R	FO	3Ws	−	++	++	−	+	−
4L	2Ws	1M	−	++	++	−	−	−
4R	NA	2Ws	−	+	+	−	+	−
5L	6Ws	2Ms	−	+++	+++	−	−	−
5R	NA	2Ws	−	+	+	+	+	−
6L	7Ws	2Ms	−	+++	+++	−	−	−
6R	NA	1W	−	+	+	−	+	−
7L	23Ws	1W	−	+	+	−	+	−
7R	NA	6Ms	−	+++	+++	−	−	−
8L	NA	6Ms	−	+++	+++	−	−	−
8R	22Ws	2Ws	−	+	+	−	−	−
9L	NA	3Ds	−	−	−	−	+	−
9R	NA	3Ds	−	−	−	−	+	−

RMB : rete mirabile, L : injection on left side of RMB, R : injection on right side of RMB, D : day, W : week, M : month (time elapsed after the first or second embolization), FBGC : foreign body giant cell, FO : feeder artery oculusion, NA : not available, + : minimal, ++ : mild, +++ : prominent, − : absent.

Table 4. Summary of angiography and histopathology findings in Group B

RMB Sample Number	Injection time (sec)	Vaso–spasm	Follow up	Angitis	FBGC	Angio–necrosis
1L	5	—	1W	—	—	—
1R	5	—	3D	—	—	—
2L	5	—	2Ws	—	—	—
3L	15	—	2Ws	—	—	—
4R	15	—	1W	—	—	—

RMB : rete mirabile, L : injection on left side of RMB, R : injection on right side of RMB, D : day, W : week, time elapsed after injecton, FBGC : foreign body giant cell, — : absent

3) Histopathology

(1) Group A (HEMA–co–MMA, 18 RMBs)

Extraction of the RMB from the cranial base was easy. Macroscopically, the RMBs in the chronic period were harder and slightly smaller than the one in the acute period.

The acute specimens (2 to 3 days after embolization, 3 RMBs)

The lumen of the blood vessel was plugged with the HEMA–co–MMA. A part of the plug was eosin－positive. Degenerated red blood cells and the infiltrate of a few round cells and fibroblasts were present. The intima (which was confirmed by immunohistochemical staining) was slightly edematous. Cells of the endothelium were partly exfoliated and falling off. Endothelial proliferation occurred and an infiltrate of round cells and bleeding were seen under the endothelium (Figure 2A). The inner elastic lamina was elongated, and most of the muscle layer was well maintained, but some thinning was seen and the staining level was reduced. No special changes were observed in the thin outer elastic lamina and adventitia (Figure 2B).

Subacute specimens (1 to 3 weeks after embolization, 8 RMBs)

First week : The HEMA–co–MMA plugged the lumen of the blood vessel, and a few infiltrates of round cells and fibroblasts appeared. In the same area, endothelial cells had fallen off and disappeared, and the inner elastic lamina had thinned, was partly disconnected, and touched the lumen directly. Bleeding was observed under the endothelium in one area. In the muscle layer of the media, there were pyknosis, decreased staining, and thinning of the layer. A part of the muscle layer lost its normal architecture and was replaced with collagen fibers. In the adventitia, some round cells were observed.

Second week : The HEMA–co–MMA that filled the lumen of the blood vessel had crystallized in only one area, and some fibroblasts and red blood cells were observed. The endothelium disappeared, and the elastic lamina was elongated, thin, and partly disrupted. The muscle layer of the media was degenerating and thinning markedly. Thin adventitia was partly disrupted, and a slight infiltrate of round cells was seen. In one place, foreign body giant cells were recognized in the blood vessel lumen (Figure 2C).

Third week : Crystallization of the HEMA–co–MMA that occupied the lumen of the blood vessel had advanced, and slight infiltration of round cells was seen. Recanalization or organization had not occurred. Fragmentation and thinning of the inner elastic lamina and thinning of the muscle layer of the media had progressed markedly, and slight round cell infiltration had occurred.

Chronic specimens (1 to 6 months after embolization, 7 RMBs)

First month : The HEMA–co–MMA had crystallized and shrunk in the lumen of the blood vessel, and infiltrated round cells were not seen. Endothelial cells had almost all disappeared, the greater part of the muscle layer of the media was replaced with collagen fiber, and the layer structure of the blood vessel was lost. The inner part of the elastic lamina was partly intact, and the thin outer part of the elastic lamina had almost disappeared.

Second month : The HEMA–co–MMA in the lumen of the blood vessel had crystallized and thin-

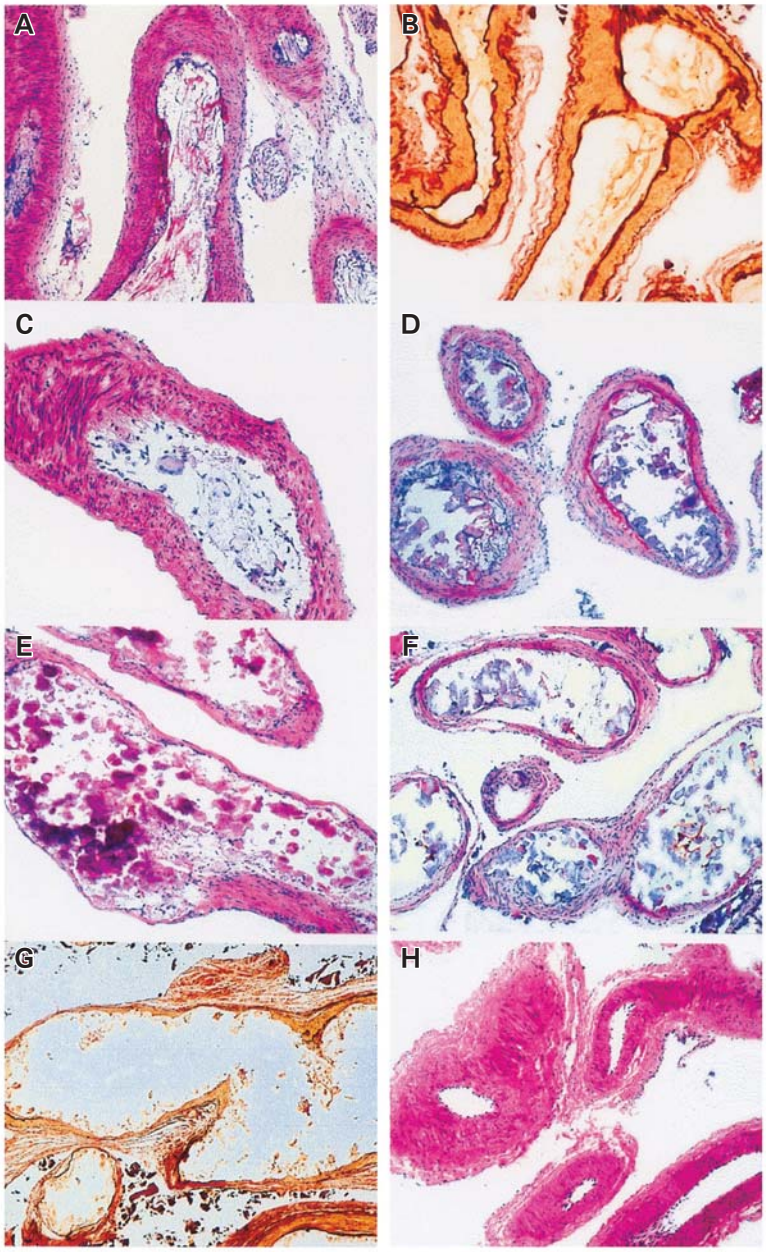

Figure 2. A：Rete mirabile from group A. 3 days after embolization. The HEMA–co–MMA has almost filled the inner side of the cavity in the blood vessel. Degenerated red blood cells and a few infiltrates of round cells or fibroblasts can be seen. Locally, thickening of the intima and bleeding under the intima are visible. (hematoxylin –eosine stain；original magnification, ×25). B：Rete mirabile from group A. 3 days after embolization. The internal elastic sheet is extended, but without any fragmentation. A thin external elastic sheet is seen. (elastica–van Gieson stain；original magnification, ×40). C：Rete mirabile from group A. 2 weeks after embolization. Round cells, fibroblasts and a few foreign body giant cells are seen in the vessel and the endothelial cells disappear.(hematoxylin and eosin stain；original magnification, ×50). D：Rete mirabile from group A. 2 months after embolization. The HEMA–co–MMA had mostly crystallized and a few round cell infiltration are seen. (hematoxylin and eosin stain；original magnification, ×25). E：Rete mirabile from group A. 3 months after embolization. The HEMA–co–MMA had almost completely crystallized and the un–thinness of the blood vessel is in progress.(hematoxylin and eosin stain；original magnification, ×25). F：Group A 6 months after embolization. Crystallization of the HEMA–co–MMA is advanced, thinning of the blood vessel wall has progressed, and the muscle layer of the media is replaced with collagen fibers. (hematoxylin and eosin stain；original magnification, ×25). G：Rete mirabile from group A. 6 months after embolization. The internal elastic sheet is thin and torn to pieces. The external elastic sheet has disappeared.(elastica –van Gieson stain;original magnification, ×20). H:Rete mirabile from group B. 3 days after injection. The endothelial cells, the muscle layer of the media, and the adventitial coat are normal. Infiltration of cells is not observed. (hematoxylin－eosin stain；original magnification, ×25)

ning of the wall of the blood vessel (especially in the media) had progressed (Figure 2D). The layer structure in the wall of the blood vessel had almost disappeared and was replaced with fibrous tissue. The inner elastic lamina was thin and almost completely disrupted, and the outer elastic lamina had disappeared.

Third to sixth months : Almost all of the HEMA-co-MMA had crystallized, the muscle layer of the media was replaced with collagen fiber, and thinning of the vessel wall was marked (Figures 2E, F, G).

When the infiltrate of round cells had reached all layers of the intima, the media, and the adventitia, we diagnosed angitis. When angitis accompanied with infiltration of neutrophils and macrophages, we diagnosed angionecrosis. These findings were not seen in all RMB cases. In all cases, the HEMA-co-MMA did not plug the most peripheral sides of the RMBs(the transition area with the internal carotid artery). The angiographic and histopathology findings for Group A are summarized in Table 3.

⑵ Group B (Solvent solution, 5 RMBs)

In 1 RMB in the acute period (3 days after embolization) and in 4 RMBs in the subacute period (1 to 2 weeks after the embolization), the endothelial cells, the inner elastic lamina, the muscle layer of the media, the thin outer elastic lamina, and the adventitia had normal angioarchitecture and no histologic changes were seen (Figure 2H). The angiographic and histopathology findings for Group B are summarized in Table 4.

Discussion

We examined in the RMB of swine the reactivity of HEMA-co-MMA with blood vessels and the effectiveness of the material as a permanent embolus for treatment of cerebral AVMs. It is safe and effective, and does not cause any problems such as angitis, cytotoxic effect and recanalization.

Treatments of AVM with liquid embolus substances have used polymerizing cyanoacrylate adhesives the polymer solutions such as n-butyl-2-cyanoacrylate (NBCA), ethylene vinyl alcohol copolymer (EVAL), and HEMA-co-MMA. The NBCA obstructs thin blood vessels and prevents recanalization, but the material is more adhesive to the catheter than HEMA-co-MMA. In comparison with NBCA, it is not so hard to incise the occluded vessels with HEMA-co-MMA.[9)12)]

The organic solvent of a polymer solution spreads over the blood vessel, and the dissolved polymer deposits and obstructs the vessels. After deposition, the polymer shrinks and the solvent and contrast medium spread.[13)] With EVAL, the reaction of the blood vessel after embolization is severe, and the risk of angionecrosis or new bleeding is high.[13)-16)] HEMA-co-MMA is used clinically as an embolic material for treatment of AVM, but a detailed examination of blood vessel reactions to it has not been done.[9)]

We followed the effects of HEMA-co-MMA injection with time. We used frozen tissue slices and isopropyl alcohol dehydration because the HEMA-co-MMA does not dissolve in isopropyl alcohol. For the basic Fuchsin-methylene blue staining, we used acetone to dehydrate at the time of embedding in the synthetic resin, and diluted the staining liquid (basic Fuchsin) with the distilled water to preserve the structure of the HEMA-co-MMA embolus. We found that the HEMA-co-MMA embolus shrank gradually and crystallized with time after the solvent and the contrast medium spread. In view of this, we expected to observe recanalization of occluded vessels but at several times after embolization the RMB could not be visualized by angiography, the blood vessel was plugged by the crystallized HEMA-co-MMA, and recanalization was not observed. The catheter did not adhere to the HEMA-co-MMA, catheter manipulation was easy, and repeated embolization with the same catheter was possible. There was no trouble with catheter manipulation with either of the polymer solutions, but solution (M) was superior for effective embolization.

The EVAL material is a medical polymer used in the dialysis membrane of the artificial kidney, and its organic solvent, dimethyl sulfoxide, can cause angitis and is toxic to nerve cells. According to Chaloupka et al, Murayama et al, and Sampei et al, concentrated ethyl alcohol or anhydrous dimethyl sulfoxide caused damage to the endothelium of blood vessels and brain tissue after they were injected into the rat carotid artery. Therefore,

ethyl alcohol should be injected at a low concentration.[2)4)17)] The 10% ethyl alcohol used in our experiments caused no histological changes and was relatively safe.

HEMA is used for soft contact lenses, and MMA is used for artificial bones. These materials and the HEMA–co–MMA polymer solution that we produced are considered safe for the human body. In this experiment, inflammatory reaction to HEMA–co–MMA was very rare and mild. Only a few round cell infiltrations were observed in the time between the acute and subacute periods, and angitis was not found. Therefore, radiotherapy or surgical intervention could be done in the early period after an embolization and is unlikely to cause complications such as hemorrhage.

The crystallization of the HEMA–co–MMA started after 2 weeks and the whole embolus was crystallized in 3 to 6 months. Even during this period, an inflammatory reaction was not seen and there was very little organization of the blood vessel. The thinning of the blood vessel wall developed and the vessel wall become fibrous in the chronic period between 3 to 6 months. Ours is the first of these phenomena.

Conclusion

We conclude that HEMA–co–MMA causes none of the problems such as angitis, cytotoxic effect and recanalization, and there is a possibility of becoming a permanent embolic material. Further investigation needs to make a conclusion for basic and clinical studies of this material.

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