Embolic materials

Shiro Onozawa[1], Hiroshi Kondo[2], Yoshiaki Katada[3], Satoru Murata[4]
Department of Radiology, Teikyo University Mizonokuchi Hospital[1]
Department of Radiology, Teikyo University[2]
Department of Radiology, Tokyo Women's Medical University Medical Center East[3]
Department of Radiology, Nippon Medical School

Introduction

Many types of embolization devices are available now, some of which have developed in the fields of neurointervention (Onyx, Glue, and detachable coils) and vascular intervention (Stentgraft), and then they were spreading in the other fields For example, Viabahn, a self-expandable stent graft (Gore & Associates, Flagstaff, AZ, USA), have developed in peripheral vascular field for the treatment of limb ischemia, but it have shown good results for the treatment of hemorrhagic vascular lesions including arterial injury and aneurysms. These developments in new embolic devises may change the strategy and techniques in management of hemorrhagic vascular lesions in all organs.

Nowadays, it is essential for successful treatment to know the characteristics of various embolic materials and to select the most adequate embolic material for each case based upon the patient's conditions, vascular anatomy, and accessibility.

Embolic materials

Gelatin sponges

Gelatin sponges are an embolic material that is frequently used to control bleeding emergencies in pelvic fractures[1], gynecological hemorrhage[2,3], hemoptysis[4,5] or blunt organ injuries[6-8] in patients without coagulation disorders. Gelatin sponge is a biologic substance made from cow or pig bone or skin, therefore still allergic potential because of heteroprotein[9,10]. Because of the biologic substance, gelatin sponges are absorbable within about 2 to 6 weeks after embolization[I]. Therefore, it is a good candidate of the embolic materials for the blunt organ injury, pelvic fractures, etc. to avoid the complete ischemia of target area. On the other hand, in coagulation disorder cases, gelatin sponge might not be effective because gelatin sponge usually requires the patients' coagulation reaction to obtain efficient hemostasis. Gelatin sponges in Japanese market are made from Australian cow bone with less biological reaction due to least endotoxin than Gelform and Spongel. There are two forms of available gelatin sponges. One is a sheet form (Serescue, Nihonkayaku, Tokyo, Japan, Figure 1a, 1b) and the other is particle form (Gelpart, Nihonkayaku, Tokyo, Japan, Figure 1c, 1d). The sheet form gelatin sponge has to be prepared by the manual cutting or pumping using 3-way stopcock. This material can be used for occlusion of relatively small vessels up

to a few millimeters. A particle form of gelatin sponge, a spherical 1 or 2 mm diameter gelatin sponge, does not require any preparation before embolization. In emergency situations, preshaped sponges reduce the procedure time to embolization and are also very helpful especially in single operator procedures.

Metallic coils, microcoils, detachable coils, and vascular plugs

These devices primarily used for isolation and/or packing of the aneurysms. Metallic coils are made of alloy includes mainly platinum, nickel or cobalt[11]. There are two types of the metallic coils. One type is provided with synthetic fibers and the other without. Fibered coils may influence the coagulation reaction of patients to occlude the vessels. Non-fibered coils do not always require the coagulation reaction however they require the dense packing in the target lesion (more than 24% of packing density in the peripheral aneurysm[12]). The delivery systems of coils are divided also into two types; one is pushable and the other is detachable. Pushable coils (Figure 2a,b) are provided only coil without any delivery system. They can be pushed by saline, coil pusher or guide wire. It is impossible to retrieve this type of coils after the coils are pushed beyond the tip of the catheter. The merit of pushable coils is less expensive than detachable coils. The detachable coils (Figure 2c-f) are attached with detachment wire. The connecting mechanisms between coils and delivery wires include mechanical, electric heating, electrolysis or hydraulic type. Due to the connecting mechanisms of detachable coils, the smoothness of the coil delivery and pushablity were different. The majority of the detachable coils have stretch resistance mechanisms (SR) mainly provided by the filament. The detachable coils should be enough resistant for repeat repositioning of coils to achieve the good packing or creating cage, otherwise the detachable coil may cause its unraveling. The coil sizes ranges from 1 to 32 mm in secondary diameter. The Amplatzer Vascular Plug family (Abbott, Chicago, IL, USA, Figure 3) is an alternative to coil embolization. AVPs are self-expanding Nitinol mesh occlusion device in plug shape with screw type detachment system, which provide the most precise positioning of the AVPs. AVPs, AVP II and AVP 4 are available in Japanese market but AVP III is not launched in Japan. AVP is single layer mesh with 4 to 16 mm in diameter. The advantage of AVP is the short landing zone compare to the AVP II. Disadvantage of AVP is longer occlusion time due to the single layer and less dense mesh. AVP II is multi-layered and multi-segmented design with 3 to 22 mm in diameter. The merit of AVP II is the shorter occlusion time than AVP because of multi-layered and multi-segmented mesh. The demerit of AVP II is the longer landing zone however the landing zone could be controllable with compression method. Both AVP and AVP II require 6Fr or larger guiding catheter or guiding sheath for device delivery. AVP 4 is alternative choice with low profile flexible mesh only requires the diagnostic catheter more than 0.038 inches inner diameter for delivering. The size of AVP 4 ranges 4 to 8 mm in diameter.

The advantage of this material is the precise occlusion of the vessels because of the detachment system with self-expanding plug design. AVP III is the other lineup of the AVP family but not available in Japanese market. AVP III is provided in Oblong cross-sectional shape with multiple layers of Nitinol mesh. According to the producer site, AVP III might provide the fastest occlusion of all the AVPs. Because of its unique design and detachment system, the AVP family can be positioned more precisely than coils, and it can be a coil or catheter anchor[13].

N-2-butyl cyanoacrylate (NBCA) glue **(Figure 4)**

NBCA is a liquid embolic material including cyanoacrylate adhesion[14,15]. There were three cyanoacrylates available before, because of the usefulness and safety reason, N-2-butyl cyanoacrylate is now widely available so called NBCA or glue[16]. Cyanoacrylates chain reaction of polymerization occur in anion condition[17]. The pure NBCA is radiolucent and reacts very quickly, therefore, ethiodized oil (Lipiodol, Guerbet, France) or Tantalum powder is mixed with NBCA to obtain the radiopaque and to control the reaction time of polymerization. NBCA is widely used for embolization procedures in patients with coagulation disorders because of its adhesive characteristics[18,19]. Once NBCA is injected in the blood vessels, NBCA started to polymerize due to anions trigger NBCA chain reaction[17]. NBCA polymerization cause inflammatory damage of the endothelium finally cause the permanent occlusion of the target vessels[20]. Anions are required to initiate NBCA polymerization, therefore, to start the injection of NBCA-Lipiodol mixture, the catheter should be rinsed with glucose to eliminate the anions in catheter lumen to avoid the NBCA adhesion in the catheter during injection. Lipiodol is usually mixed with NBCA to control the polymerization time[3]. The NBCA:Lipiodol ratio is 1:1 to 1:5, with a higher NBCA content having a shorter polymerization time and higher Lipiodol content providing a longer polymerization time but a more viscous liquid. The appropriate ratio of the mixture is important because the mixture with high NBCA ratio may not reach the bleeding point due to immediate polimerization. The major injection method is continuous column injection[21], which means NBCA injection continuously as a column without reflux of NBCA. Sandwich injection is alternative method of the NBCA injection. Some amount of the NBCA is loaded in the catheter and consecutively glucose pushes out the loaded NBCA. To switch the NBCA and glucose consecutively, 3-way stopcock is useful. Pumping injection is sometime reported. In this method, NBCA is injected as a droplet. Wedged injection method can provide a longer polymerization time. In this method, catheter tip is wedged into the small artery before NBCA injection, then, both of the catheter and the artery wedged are filled by glucose. Because of the wedging catheter, the anion contained in the blood is eliminated. Therefore, NBCA does not polymerize until it reaches the target lesion or collateral blood flow. Balloon assisted NBCA, B-Glue technique was reported by

Hamaguchi et al[22]. as an alternative to wedged injection, and it utilizes a micro-balloon catheter, which provides a low profile and high trackability. B-Glue technique is especially useful in torturous feeding arteries, which are not appropriate for the wedge injection technique. Some physicians use very low concentrated NBCA solutions with 1:9 or 1:10 mixture ratios which shows similar hemodynamic behaver to 100% Lipiodol, flowing into the target lesion. In my personal experience, postpartum hemorrhage is the best candidate for very low concentrated NBCA.

Stent graft (Viabahn) (Figure 5)

Stent graft is the covered stent with PTFE or other membrane. There are self-expandable stent graft and balloon-expandable stent graft in the world market. However, Viabehn (Gore), which is the heparin bonded self-expandable stent graft, is only available for peripheral vascular lesions in Japan. This stent graft is indicated as an alternative device for hemorrhage in Japan, but only traumatic or iatrogenic arterial injuries in thoracic or abdominal regions, with the exceptions of the aorta, coronary arteries, brachiocephalic trunk, carotid arteries, vertebral arteries, and pulmonary arteries are covered by health insurance. Therefore, true aneurysms are not an indication. In bleeding cases, spastic arteries are often observed. Therefore spasm may narrow vessels and make size selection difficult. The stent graft delivery may present problems in emergency practice as a 6Fr or wider guiding catheter or guiding sheath is used to deliver the stent graft. If the injured artery is proximal to the major aortic branches, the delivery is not very difficult. However, if a distal vessel injury occurs, stent graft delivery is more complicated. Also dual antiplatelet therapy (DAPT) is required after stent graft deployment to reduce the risk of thrombotic occlusion of the stent graft, but may be problematic in traumatic patients. The costs of the stent graft and the placement procedure are high.

Others

Onyx (Figure 6) is also liquid embolic material consisting of ethylene vinyl alcohol copolymer (EVOH), which is a plastic polymer dissolved in a potent organic solvent, dimethyl sulfoxide (DMSO). When Onyx is expressed from the microcatheter it comes into contact with the blood, the solvent disperses and the plastic polymer returns to its solid form. This embolic agent cannot be deemed to be a glue as it does not have adhesive properties in contact with arterial walls but only properties of "filling" the vascular lumen. The major advantages of this liquid compared to the glue are its non-adherence, progressive solidification, cohesiveness, high vascular penetration and a very weak inflammatory effect on the endothelium. Because of the toxicity and irritative of DMSO, Onyx should be injected very slowly (less than 0.3 ml/minutes). DMSO is an organic solvent has potential risk of the catheter breakage. Therefore, the appropriate catheters should be used for Onyx injection. Onyx has

developed as an embolic material for embolization of cerebral arteriovenous malformations (AVMs). However, it is now widely used for peripheral lesions including AVMs or endoleaks after Aortic stentgraft. Microspheres are also the embolic material mainly for cancer embolization, therefore, details of these materials would be omitted this section. They are the spherical form embolic materials. The advantage of these materials is well-controlled size distribution, possible drug delivery system and permanent embolization. Microspheres in Japanese market are DC beads (Figure 7a), Hepasphere (Figure 7b)and Embosphere (Figure 7c). Under Japanese health insurance coverage, microspheres have indication for hepatocellular carcinoma, hypervascular tumors and AVMs. Because the microspheres can pass through the shunts of AVM lesions to cause pulmonary arterial embolism, they must be used with caution.

Choosing embolic materials

The most important information to guide the selection of embolic devices is patient coagulation status and the size of target vessel. A Japanese Society of Interventional Radiology survey found that the majority of interventional radiologists would choose NBCA as the embolic material for patients with coagulation disorders. Determining the size of the target vessel before the procedure was also considered important. The correct diagnosis (e.g. to distinguish the pseudoaneurysms from the true aneurysms), and the accurate knowledge of the available embolic materials and devices are the most important factors in planning. In this section, the principle of the embolic materials is provided.

Conclusion

In this section, the most common embolic materials and devices have been introduced, and many are available in Japan. To select embolic devices, the best alternative for the patient at that moment must be considered.

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a | b
c | d

Figure 1: Gelatin sponges in Japanese market

a: Photo of Serescue (Nippon Kayaku, Tokyo, Japan). Its size is about 2.5 x 2.5 cm with 1cm thickness.

b: Gelatin sponge particles after manual cutting of Serescue. Particle size is controllable by each physician. To prepare the particle, it takes about 1 to 5 minutes. In emergency situations, the preparation might be time consuming.

c: Photo of Gelpart (Nippon Kayaku, Tokyo, Japan). The spherical gelatin sponge particle distributed in a Vial in 1 and 2 mm in diameter.

d: Magnified image of the Gelpart in 2 mm in diameter

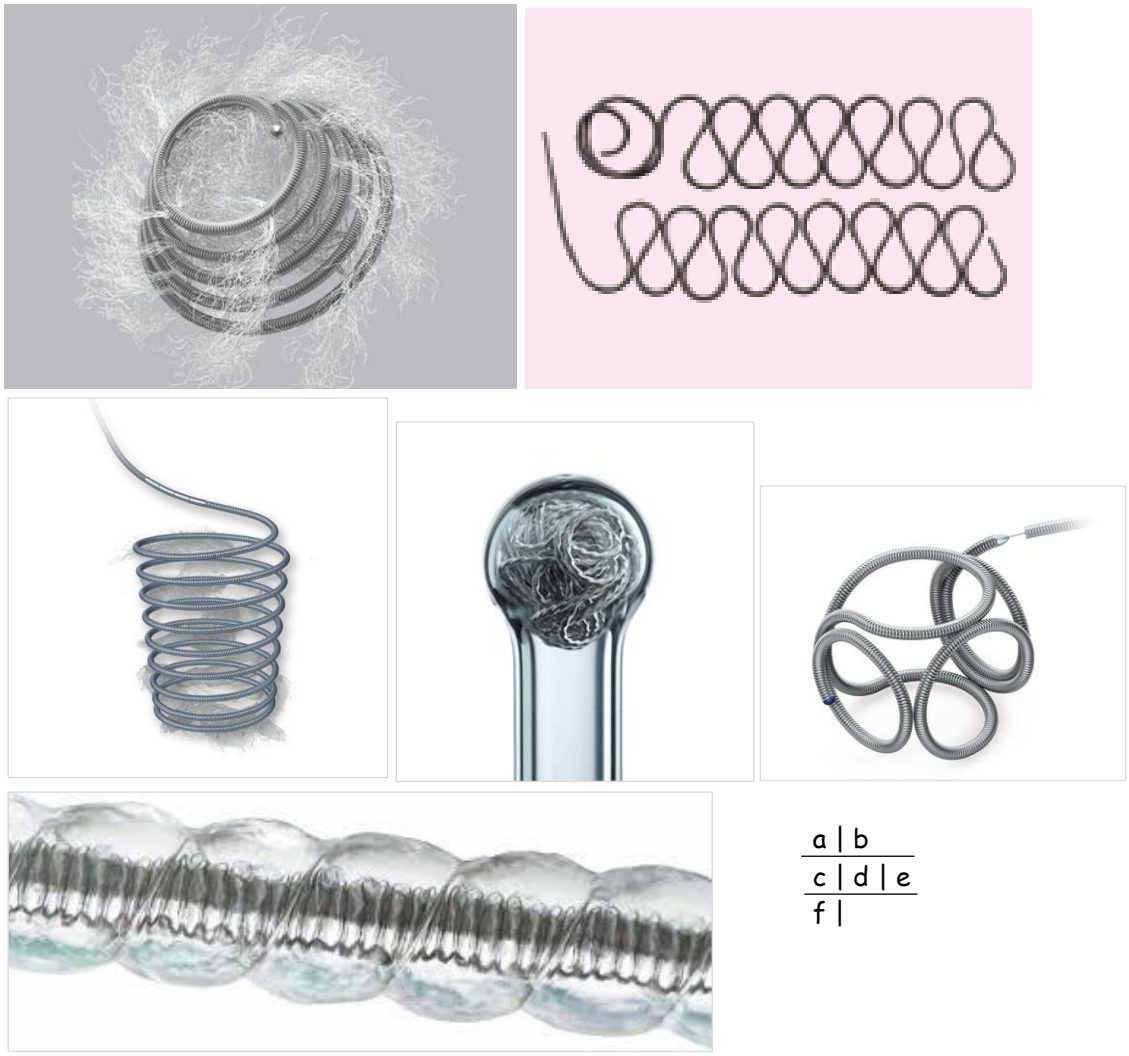

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Figure 2: Metallic coils in Japanese market

a: Tornado coil (COOK medical, Bloomington, Indiana, USA). Pushable coil with fiber fixed in tornado shape.

b: C stopper (Piolax medical device, Yokohama, Japan). Pushable coil without fiber.

c: Fibered IDC (Boston scientific, Marlborough, MA, USA). Detachable coils with mechanical detachment system. There are fibered and non-fibered types available.

d: Deltamaxx (Johnson and Johnson, New Brunswick, New Jersey, USA). Detachable coils with electric heating detachment system. Delta shape coils.

e: Target coils (Striker, Kalamazoo, MI, USA). Detachable coil with electrolysis detachment system.

f: Azur (Terumo, Tokyo, Japan) after hydrogel expanded. Detachable coils with electric heating detachment system. Expandable hydrogel covers coils or fill inside the coils. The hydrogel around coil expand 4 to 5 times more than original size of coils distribute the wider filling volume.

Figure 3: Amplatzer Vascular Plug family (Abbott, Chicago, IL, USA). AVP, AVP II and AVP 4 are available in Japan.

Figure 4: NBCA. Liquid embolic material in plastic tube.

Figure 5: Viabahn (W. L. Gore & Associates, Inc., Flagstaff, Arizona, USA). Stentgraft with heparin bonding inside the stentgraft now only available in Japanese market for vascular lesions.

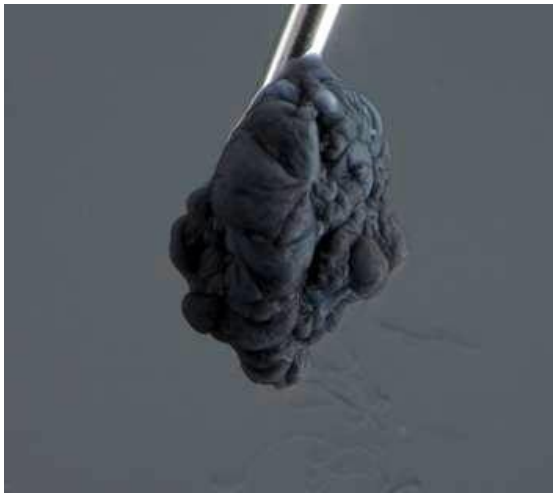

Figure 6: Onyx (Medtronic, Minneapolis, Minnesota, USA). Liquid embolic material contains ethylene vinyl alcohol copolymer (EVOH) and dimethyl sulfoxide (DMSO).

Figure 7: Microspheres in Japan.
a: DC bead (BTG PLC, London, GB). Drug eluting beads with indication for hypervascular tumors and AVMs.
b: Hepasphere (Nippon Kayaku, Tokyo, Japan). Drug eluting beads with indication for the hypervascular tumor and AVMs.
c: Embosphere (Nippon Kayaku, Tokyo, Japan). Brand embolic microspheres with indication for hypervascular tumors and AVMs.

a | b
c