Experimental Investigations Concerning a New Liquid Embolization Method: Combined Administration of Ethanol-estrogen and Polyvinyl Acetate

Takayuki SUGAWARA, Akira TAKAHASHI, Ching Chan SU*, Toshihiro SUGA* and Takashi YOSHIMOTO*

Department of Neurosurgery, Kohnan Hospital, Sendai; *Division of Neurosurgery, Institute of Brain Diseases, Tohoku University School of Medicine, Sendai

Abstract

A new embolization agent combining ethanol-estrogen and polyvinyl acetate was evaluated angiographically and histologically in 18 canine renal arterial systems. Peripheral vessels of less than 100 μm diameter were obliterated by thrombus induced by ethanol-estrogen, and larger vessels were obliterated by polyvinyl acetate casts and/or thrombus. This embolization method is easily controlled and has fewer adverse effects, so is suitable for intravascular applications, especially in the head and neck regions.

Key words: estrogen, embolization, intravascular surgery, polyvinyl acetate

Introduction

Transcatheter intra-arterial embolic occlusive therapy is increasingly used in patients with vascular malformations and neoplasms. The choice of embolization agent is an important issue in this technique. Various agents have been developed and tested in animal models, or applied clinically. In general, liquid embolization agents are more suitable than solid types, because the latter do not achieve complete obliteration, frequently resulting in recanalization. Cyanoacrylate liquid embolization agents have been used widely in head and neck lesions. However, problems have arisen, such as incomplete occlusion and recanalization.

We previously described the use of ethanol-estrogen for experimental progressive obliteration of the arterial system from the peripheral capillaries to the proximal renal artery. This progressive occlusion and degeneration of endothelial cells also caused undesirable tissue reactions, such as edema and petechial hemorrhage. Such undesirable reactions can possibly be reduced by another material obstructing the proximal blood flow shortly after infusion of ethanol-estrogen. Here, we report the use of polyvinyl acetate combined with ethanol-estrogen for the embolization of the canine renal arterial system evaluated by angiographic and histological methods.

Materials and Methods

Polyvinyl acetate is a polymer (C₄H₅O₂, molecular weight 43,000) soluble in greater than 55% ethanol (Fig. 1). Metrizamide and propylene glycol were added to this polymer for radiopacity and as a disinfectant, respectively. Three polyvinyl acetate solutions (PVac-1, 2, and 3) were prepared with various concentrations of polymer and ethanol (Table 1). The resultant PVac had sufficient radiopaque agent (100 mg/ml) for easy fluoroscopic control at injection. The solutions became gelatinous (reprecipitated) immediately upon contact with an aqueous environment but without adhesion to the catheter (Fig. 2). To prevent reprecipitation inside the catheter, 25% ethanol was pre-injected in a volume equal to the dead space of the catheter (0.7 ml).

Eighteen mongrel dogs were anesthetized with intravenous thiopental 15 mg/kg and pentobarbital 5–10 mg/kg, and maintained on spontaneous respira-
tion. Pre-embolization renal angiograms were obtained by the femoral route using a 5 F catheter. A unilateral renal artery was embolized using a 5 F double-lumen balloon catheter, with the tip positioned in the orifice of the artery. Embolizations were carried out with the balloon inflated.

The animals were divided into three groups. In the control group, two animals received sham embolization using normal saline (0.3 ml/kg) infused over 20 minutes. The PVac group contained six animals. Embolization was carried out using the three PVac (2.5-3.5 ml) infused over 4-7 minutes under fluoroscopic control in two animals each. The combined group contained 10 animals which all received embolization with ethanol-estrogen (0.3 ml/kg) infused over 20 minutes, followed by infusion of PVac-2. The catheter balloon was left inflated for 10 minutes after completion of infusion, then deflated and removed. Selective renal angiograms were performed 15 minutes and 1 hour after embolization. All animals were allowed to recover from anesthesia.

Table 1 Composition of various PVac

<table>
<thead>
<tr>
<th></th>
<th>PVac-1</th>
<th>PVac-2</th>
<th>PVac-3</th>
</tr>
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<tbody>
<tr>
<td>Polyvinyl acetate</td>
<td>209</td>
<td>190</td>
<td>175</td>
</tr>
<tr>
<td>Ethanol</td>
<td>337</td>
<td>340</td>
<td>343</td>
</tr>
<tr>
<td>Distilled water</td>
<td>318</td>
<td>330</td>
<td>340</td>
</tr>
<tr>
<td>Metrizamide</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>5</td>
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</tr>
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Values are expressed as mg/ml.

Animals in the control and PVac groups were sacrificed 4 days after embolization. Animals in the combined group were sacrificed after 1 hour (n = 2), 4 days (n = 4), 1 month (n = 2), and 3 months (n = 2). After perfusion fixation with 10% phosphate buffered formalin, the kidneys, adrenal glands, abdominal aorta, and vena cava were removed en bloc. Specimens embolized with PVac were made into frozen sections and stained with ethanol-free HE to prevent dissolution of PVac.

Results

No animal showed any outward sign of abnormality during the observation period. Autopsy revealed no abnormalities or infarctions in the intrathoracic or abdominal organs.

Angiograms demonstrated no changes in the control group. In the PVac group, polymer was observed at the catheter tip at the end point of PVac-3 infusion. However, shortly after balloon deflation, fluoroscopy showed that the PVac-3 cast was propelled to the distal main trunk arteries. In contrast, no such movement was observed in PVac-1 or 2-treated animals after balloon deflation (Fig. 3). Angiograms 4 days after embolization revealed occlusion of the renal artery in all animals. In the combined group, total obliteration was visualized after removal of the balloon catheter and in all follow-up angiograms (Fig. 4).

No morphological changes in the vessels or renal tissue occurred in the control group. In the PVac and combined groups, polyvinyl acetate was observed as a yellow material within the arteries. In PVac-1-treated animals, polyvinyl acetate was distributed from the renal artery to the interlobular arteries. However, the peripheral arterioles and capillaries

Fig. 1 Solubility of polyvinyl acetate (1 gm) in ethanol-water mixtures. ○: completely homogeneous solution, △: incompletely homogeneous solution, ×: gelatinous precipitate, ●: PVac (1: PVac-1, 2: PVac-2, 3: PVac-3).

Fig. 2 PVac reprecipitates to form a gelatinous membrane (arrowheads) on contact with saline. PVac is easily injected through a 26 gauge tuberculin needle.

Fig. 4 No morphological changes in the vessels or renal tissue occurred in the control group.
were not obliterated. The nuclei of the glomeruli and tubules were not resolved, and there were some inflammatory cells and hemorrhage at the subcapsular cortex. In PVac-2-treated animals, polyvinyl acetate was observed in arteries larger than 100 μm in diameter. The nuclei of the glomeruli and tubules were not resolved. In PVac-3-treated animals, polyvinyl acetate was observed in the interlobar arteries, the glomerular capillaries, and the venules (Fig. 5).

Complete renal arterial obliteration was observed in the combined group. Thrombosis was observed in arteries with a diameter of less than 100 μm, and polyvinyl acetate was present in larger arteries. The renal artery and renal arterial trunk were completely obstructed by a mixture of polyvinyl acetate and thrombus (Fig. 6).

Complete renal infarction was observed 4 days
after embolization in the PVac group, and at all times except 1 hour after embolization in the combined group. The macroscopic appearance of the canine kidney in the combined group showed marked shrinkage (Fig. 7). However, no undesirable tissue reactions, such as foreign body giant cell reactions, were observed in the infarcted parenchyma.

Discussion

The ideal embolization material for treating vascular malformations and tumors should achieve: 1) a diffuse embolizing property which induces obliteration from artery to capillary without propagation into veins; 2) suitability for introduction through a tiny catheter as only superselective catheterization can preserve normal tissue circulation; 3) easy control with radiopacity, long infusion time to control the embolizing volume, and no adhesion to the catheter; 4) nontoxicity, biological inertness, and low reactivity to the normal parenchyma around the target lesion; 5) no recanalization following the embolization; and 6) easy resection of embolized tissue.

Cyanoacrylate glue (isobutyl-2-cyanoacrylate: IBCA, or N-butyl cyanoacrylate) is considered the best liquid embolization agent, but there are technical difficulties due to incomplete embolization. Recently, Vinuela et al. reported on the effectiveness of this agent in a clinical review of long-term results in 30 patients with partially embolized arteriovenous malformations (AVMs). The main technical problem was related to inaccurate delivery of IBCA into the AVM nidus. In our opinion, this problem is related to the characteristics of IBCA, especially the tendency to polymerize too quickly. Therefore, control is difficult to achieve during embolization. Klara et al. made a morphological study of AVM embolized using IBCA, finding a lattice structure and microchannels within the IBCA embolus. Rao et al. observed recanalization of AVMs following complete obliteration using IBCA. These studies suggest...
that the IBCA embolization capability is incomplete. There are also more fundamental problems involved in the use of single liquid polymer embolization materials. One is the volume change which occurs when a liquid material polymerizes to a solid. Another is the pulse of the arterial blood flow, which may result in a gap between the solidified embolus and the arterial wall. In addition, the embolization material and blood might mix if the blood flow is not controlled. Such gaps and temporary coagulated blood could cause recanalization following embolization. Furthermore, the whole vascular system, which contains microcirculation (capillaries) and large arteries, could not be obliterated if a single liquid embolization material is used. Venous occlusion or pulmonary embolism might occur if the liquid embolization material passes through the venous side, or proximal occlusion if a liquid agent solidifies at the proximal side, causing development of collateral flow to the target lesion.

Combined administration of different types of embolization agents, such as ethanol-estrogen followed by PVac, has not been previously reported. This method might solve some problems involved in the use of a single embolization agent. We reported that the embolization effect of ethanol-estrogen was as strong as that of absolute ethanol and that acute obliteration after the infusion of ethanol-estrogen occurred initially in small vessels (<10 µm in diameter), then spread to larger vessels. This progressively occlusive character of ethanol-estrogen has some unique thrombogenic or self-inflicted properties. However, acute vascular reaction occurred after infusion of ethanol-estrogen, i.e., infiltration of microscopic red blood cells. Our study using PVac has shown that this can be prevented by occluding the main arterial flow using an additional liquid embolization agent.

Peregrin et al. first reported polyvinyl acetate as an embolization agent in 1984. We tested it in vitro and in vivo, and found a better combination with more diluted ethanol than the original 95% ethanol. We also use a different radiopaque material, metrizamide instead of lipiodol, to make a homogeneous radiopaque solution. The polyvinyl acetate used in our study had a molecular weight of 43,000 and structural formula of n = 500. This type of polyvinyl acetate was soluble in greater than 55% ethanol in our in vitro study. The in vivo study showed the characteristics of PVac changed with the concentration of ethanol and polymer: PVac-3 passed through the capillaries with cast migration after removal of the double-lumen balloon catheter; PVac-2 reached arteries larger than 100 µm in diameter; and PVac-1 reached the interlobular arteries without cast migration. We selected PVac-2 for combined administration with ethanol-estrogen, because it did not pass to the venous side in the canine renal arterial system and it could be administered through a tiny catheter, such as a floppy-tip leak balloon catheter. Another type of PVac might be more useful in other vascular systems. Other polyvinyl acetates (n = 50-5000) are available for other vascular lesions, for example flow lesions or components of the vascular structure. The PVac we used caused fewer parenchymal reactions, such as foreign body giant cells, during the follow-up period. We suggest that PVac is much more biologically inert and chemically stable than other liquid agents.

The physical, chemical, and biological properties of the ethanol-estrogen and PVac combination tested in our animal experiments are suitable for intravascular application, with fewer adverse tissue reactions, and provide a suitable embolization method for intravascular treatment.

References

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Address reprint requests to: T. Sugawara, M.D., Department of Neurosurgery, Kohnan Hospital, 4–20–1 Nagamachi-minami, Taihaku-ku, Sendai 981, Japan.

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