Obliteration of experimental aneurysms in dogs with isobutyl-cyanoacrylate

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Experimental cervical carotid aneurysms in dogs are obliterated with isobutyl-cyanoacrylate (IBCA) injected under direct vision into the aneurysm. Reflux of IBCA into the artery was prevented by inflating either a latex or a Silastic balloon in the carotid artery at the level of the neck of the aneurysm. This balloon was introduced through a catheter advanced into the common carotid artery by femoral catheterization. The Silastic balloon was found to be much more effective than the latex balloon in preventing spillage of IBCA into the lumen.

KEY WORDS • experimental aneurysm • intracranial aneurysm • extracranial carotid aneurysm • balloon catheter • isobutyl-cyanoacrylate

INJECTION of isobutyl-cyanoacrylate (IBCA) into berry aneurysms at open craniotomy by stereotaxic procedures or with intraluminal balloon catheters has not become a practical clinical method of treatment because of the high risk of spillage of IBCA through the neck of the aneurysm, with consequent embolization of cerebral vessels. It is proposed that, after direct injection of IBCA into the aneurysm sac, spillage of IBCA into the lumen of the artery might be prevented by intra-arterial inflation of a latex or Silastic balloon to temporarily occlude the neck of the aneurysm during the IBCA injection. The following experiments were conducted to study the feasibility of obliterating aneurysms using this procedure.

Materials and Methods

Eleven conditioned dogs weighing 20 to 30 kg each were used in the present study. The dogs were anesthetized with intravenous ketamine HCl (15 mg/kg) and sodium pentobarbital (30 mg/kg). The animals were then intubated and allowed to breathe spontaneously. Further doses of pentobarbital were injected when necessary. The operative procedures were performed under sterile conditions.

Experimental aneurysms were created in two steps. At the first operation, using the operating microscope, a fistula approximately 10 mm in diameter was created between the common carotid artery (CCA) and the external jugular artery by a side-to-side anastomosis. At the second operation 7 days later, the fistula was exposed and two ligatures were applied on the vein, one proximal and one distal to the anastomosis, creating a venous pouch aneurysm of approximately 2.5 cm x 1.5 cm (Fig. 1). At this time, the femoral artery was punctured and a No. 8 French catheter was positioned into the CCA below the aneurysm. Angiography was performed before and after injection of IBCA into the venous sac as described below. The contralateral side was treated in the same way 1 or 2 weeks after comple-
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FIG. 2. Left: Angiogram showing a carotid artery aneurysm with constriction of the artery at the level of the aneurysm neck. Right: Occlusion of the aneurysm with IBCA. The angioplastic effect of the balloon has caused disappearance of the constriction of the artery.

FIG. 3. Left: Angiogram showing a carotid artery aneurysm before treatment. Constriction of the artery is seen at the level of the neck. Right: Angiogram of the aneurysm after treatment with complete obliteration of the pouch with IBCA. The angioplastic effect of the balloon has caused disappearance of the constriction of the artery.

It was soon realized that the latex balloon was not stiff enough to prevent the passage of IBCA through the neck of the aneurysm. Consequently, the next 14 aneurysms were treated with a Meditech angioplastic double-lumen balloon,§ which, when inflated with 2 ml of Conray 60, was 6 cm long and 4 mm wide. The metallic markers at each extremity of the balloon allowed accurate positioning of its middle part which was exactly at the level of the aneurysm neck. This balloon was also greased before use. Before the balloon was inflated, an IBCA mixture was prepared of 1.5 gm tantalum powder, 0.5 ml Pantopaque, and 2 ml IBCA. The mixture was blended well and aspirated through a No. 25 needle into a 3-ml Luer-lock plastic syringe. This small-gauge needle was used to prevent aspiration of lumps of tantalum powder into the syringe before injection. A No. 22 needle previously filled with 5% dextrose in water (D5W) was then adapted to fit the 3-ml syringe of IBCA. It was necessary to fill the needle with D5W in order to prevent blood from coming in contact with the IBCA when the aneurysm was punctured. If a drop of blood was in contact with a drop of IBCA inside the needle, the needle became occluded and injection of IBCA into the aneurysm was not possible. The venous pouch was then punctured at one of its poles with the needle as parallel as possible to the axis of the artery.

* No. 8 French Cordis sheath manufactured by Cordis Corp., Miami, Florida.
† No. 9 latex balloon manufactured by Ingenor Laboratoires, 70 Rue Orfila, 75020, Paris, France.
‡ Silicone grease manufactured by Dow Corning Corp., Midland, Michigan.
§ Double-lumen balloon manufactured by Meditech Inc., 150 Coolidge Avenue, Watertown, Massachusetts.
¶ Tantalum powder obtained from Kenametal, One Lloyd Avenue, Latrobe, Pennsylvania; IBCA obtained from Ethicon, Somerville, New Jersey.
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The IBCA injection was monitored under fluoroscopy. The aneurysm was completely filled in 3 to 4 seconds, which corresponds to the solidification time of IBCA. The criteria for successful obliteration of the aneurysm were: 1) absence of IBCA leakage into the carotid artery through the neck of the pouch during injection; 2) a whole aneurysm forming a hard mass without leakage of blood; 3) easy deflation and removal of the balloon after embolization; 4) absence of IBCA in the carotid artery; 5) complete occlusion of the neck of the aneurysm on the control angiogram after embolization; and 6) patency of the carotid artery after embolization. Figures 2 and 3 illustrate a typical angiographic “successful” result.

Embolic complications from clotting of blood below the balloon were avoided by systemic heparinization using a technique adapted from a previously described clinical practice. When the Cordis sheath was positioned in the femoral artery, a bolus of 1000 units of heparin was injected and this was repeated every hour. Additionally, the Cordis sheath and catheter were continuously flushed with 3000 units of heparin in 500 cc of saline using a pressure bag. This was done in 18 of the 22 procedures. The two dogs that were sacrificed immediately after embolization of their second aneurysm were not anticoagulated. Before the Cordis sheath was removed, anticoagulation was reversed with protamine sulfate.

The second CCA in each dog was generally treated after a 1-week interval. The patency of the first CCA treated was always checked angiographically at the time of the contralateral treatment 1 week later. Nine dogs were sacrificed 1 or 2 months after the second treatment. Two dogs were sacrificed immediately after embolization of the second aneurysm.

The arteries were perfused at a physiological pressure of 120 mm Hg with 1000 to 2000 cc of 0.1 M phosphate-buffered 2.5% glutaraldehyde (pH 7.4), through a catheter positioned in the ascending portion of the aortic arch, as previously reported. The CCA’s and aneurysms were removed and sent to the Mixter Laboratory for Ultrastructural Research of the Neurosurgical Service.

After glutaraldehyde fixation, the vessels were placed in the same phosphate buffer containing 5% sucrose to maintain isotonicity prior to spreading and postfixation. They were then opened longitudinally and sutured to 24 × 30-mm Thermanox plastic cover slips, then postfixed with 2% osmium tetroxide in distilled water for 2 hours. The vessels were then dehydrated through a graded ethanol series into acetone and then critical-point dried in a Samdri critical-point device using carbon dioxide as a transition fluid. In order to preserve the appearance of the IBCA, absolute ethanol was substituted for the acetone. The critical-point dried vessels were sputter-coated with platinum and examined in a JEOL 35S scanning electron microscope operating at 25 kV. Photographs were obtained with Polaroid 4 × 5 Type 55 P/N film.

**Results**

The results are summarized in Tables 1 and 2. We separated the aneurysms into two groups: Group I consisted of eight aneurysms in which the artery was temporarily occluded with a latex balloon, and Group II included 14 aneurysms in which the artery was occluded with an angioplastic Silastic balloon. In both groups, the IBCA was injected into the venous pouch in a similar way.

**Group I Aneurysms**

The aneurysm was totally occluded with IBCA in seven of the eight cases in Group I. In one case, the aneurysm was partially occluded and the control angiogram showed that the neck of the aneurysm was not totally occluded. Only two results were classified as good according to the criteria described previously. It appeared that the latex balloon (which has a very thin wall) could not adequately prevent the leakage of the IBCA into the carotid artery through the neck of the aneurysm, particularly near the completion of the embolization when the venous pouch was almost entirely obliterated. Furthermore, the inflated balloon bulged into the aneurysm through the neck, decreasing the chance of total obliteration of the neck of the pouch. This herniation of the balloon through the aneurysm neck is also due to the thinness of the latex wall of the balloon. It is doubtful that a thicker latex balloon would completely avoid this phenomenon because even the much stiffer Silastic angioplastic balloon produces a minimal bulge of the balloon at the level of the aneurysm neck.

**Group II Aneurysms**

In the 14 Group II aneurysms the angioplastic Meditech balloon described above was used. If the pressure of inflation of the balloon does not exceed 6 atm, the
diameter of the balloon will not exceed 4 mm, which corresponds roughly to the diameter of the CCA of the dog. However, it is important to adapt the diameter of the balloon to the diameter of the carotid artery. In one dog with a wide CCA, the diameter of the balloon was a little too small and there was leakage of IBCA through the aneurysm neck with resulting occlusion of the carotid artery after removal of the balloon. Nevertheless, in most cases the Silastic balloon became very stiff when inflated and successfully prevented reflux of IBCA. The carotid blood flow was preserved in 10 of the 14 cases. One of the instances of carotid occlusion occurred when the balloon was too small for the diameter of the artery. In two other cases, the carotid artery was patent with no obvious stenosis immediately after the injection of IBCA and removal of the balloon, but the artery was found to be thrombosed when the dog was sacrificed 1 or 2 months later. In the last case, the Silastic balloon was too big for the diameter of the artery, with subsequent tearing of the carotid artery at the level of the aneurysm neck. This aneurysm was not treated and the carotid artery had to be ligated. The previously silicone-greased balloon could be pulled down easily after embolization in all cases except in the dog in which the size of the balloon was inadequate for the diameter of the artery.

One of the unexpected findings during this study was the frequent dilatory effect of the angioplastic Silastic balloon (Fig. 3) which was found in 11 of the 14 cases. This phenomenon was most evident when the diameter
of the artery was narrowed below, above, and at the level of the neck of the aneurysm.

None of the dogs had abnormal clinical symptoms. In some cases, IBCA could be seen partially bulging through the neck of the aneurysm. The importance of this phenomenon will be discussed later.

Pathological Results

Figures 4 to 9 illustrate the typical anatomical features seen after experimental aneurysm occlusion by IBCA. The surface of the carotid artery as well as the IBCA was covered by endothelium. Occasional protrusions were seen, which were covered by endothelial cells (Fig. 4). Endothelialized strands of IBCA were sometimes seen entering the vessel lumen oriented in the direction of blood flow. Indentations were sometimes seen, which were also endothelialized. The tissue reaction to IBCA 2 months after embolization was unremarkable. The tissue in contact with the IBCA consisted of homogeneous vacuolized cells, which appeared to be mesenchymal in origin (Fig. 5).

The area of vessel directly under the balloon became desquamated and thrombogenic. Light and transmission microscopy demonstrated tears between smooth-muscle cells in the media in this area. In areas progressively removed from this site, more corrugated endothelium was present. This corrugated pattern is typical of that found in vasospasm.5,8

The initial appearance of polymerized IBCA is that of a smooth-surfaced material with many smooth projections (Figs. 6 and 7). The tissue that it touches is rough-surfaced and thrombogenic, due to desquamation which probably occurs during the inflation of the balloon. Four hours after the introduction and polymerization of IBCA, platelets and erythrocytes are adherent to its surface (Fig. 8). This adherence is different from that seen on the adjacent desquamated carotid artery. The platelets have extended pseudopodia and are in the process of flattening (Fig. 9). Endothelial cell migration presumably occurs from normal endothelium at the periphery of the desquamated vessel, which eventually covers the platelet pseudoendothelium and the IBCA surface. The regions of thrombus location seen in these vessels are either sites subjected to mechanical trauma, such as suture sites, or areas of incomplete endothelialization.

Discussion

Certain aneurysms cannot be clipped for a variety of technical reasons. Previous experimental work10 has shown that when IBCA is injected into an aneurysm at surgery, it tends to leak through the neck of the aneurysm unless the flow of the patent artery is momentarily reduced or interrupted. It would be useful to be able to obliterate the neck of the aneurysm with an intraluminal balloon as the pouch is injected with IBCA. Unfortunately, the Meditech balloon cannot be used in cere-

Fig. 6. Low-magnification scanning electron micrograph of the luminal surface of a carotid artery 1 hour after introduction of IBCA. Note the shape of the neck of the experimental aneurysm and the poorly structured polymerized IBCA. Some strands extend into the bloodstream and represent IBCA which had adhered to the balloon. The heparin therapy administered to the animal may be responsible for the lack of thrombus. × 7.

Fig. 7. High-magnification scanning electron micrograph of the IBCA-tissue interface from the same animal as depicted in Fig. 3. Note the smooth surface of the polymer and the desquamated carotid artery (right) with adherent platelets and erythrocytes. × 1020.
bral vessels since it is too stiff to navigate through the petrous and cavernous portions of the carotid artery.

A latex balloon attached to the tip of a small tubing could navigate into the cerebral vessels and could transiently occlude the neck of an aneurysm. The risk of the balloon bulging through the aneurysm neck and IBCA escaping through the neck is too great to be acceptable. Therefore, the potential clinical use of the technique herein described is limited to aneurysms originating on a straight vessel such as the carotid artery in the neck. In spite of the care taken to prevent leakage of IBCA through the neck of the aneurysm, it is impossible to avoid an irregular surface of solidified IBCA. Protrusion of IBCA into the lumen of the artery rarely occurs because the Silastic balloon is very stiff and bulges minimally into the aneurysm through its neck. The angioplastic balloon induces an undesirable effect by creating de-epithelialization of the intima and tears of the media. However, epithelialization of the area of the aneurysm neck filled with IBCA and of the area of the artery compressed by the angioplastic balloon occurs after 1 month.

Our scanning electron microscopic observations confirm an earlier histological report that endothelialization occurs over intravascular IBCA. Zanetti and Sherman also noted a benign fibrotic tissue reaction to IBCA 3 months after aneurysm occlusion with this agent. Our observations 2 months after introduction of IBCA into the blood stream are identical. Endothelial cell capacity to cover foreign material in the blood stream is mediated by platelet aggregation and adherence. Cells of mesenchymal origin grow over these platelets. This fibrous tissue becomes vascularized and serves as a substrate for endothelial cell growth. The temporal course of endothelial cell migration over desquamated vessel wall is similar to that seen in microvascular anastomoses, temporal cerebral artery occlusion, and carotid endarterectomy.

Some regions of the neck of the occluded aneurysm were not completely endothelialized. We attribute this to two possible factors. First, during the inflation of the balloon prior to IBCA injection, desquamation could have occurred in areas adjacent to the neck. The extent of desquamation may vary from vessel to vessel. A larger area of desquamation would require a longer time period for endothelial cell migration to cover all such areas. Second, as seen with intravascular Dacron, the total surface area of foreign material may be too large to permit total endothelialization. Sauvage, et al. have found that a Dacron prosthesis implanted for over 20 months in the femoral artery of a patient was endothelialized over only 32% of its area. We do not
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have a definite explanation for the two cases where the artery was perfectly patent and wide after embolization, and yet was found to be thrombosed 1 or 2 months later. It can only be postulated that the de-epithelialization of the intima secondary to the angioplastic effect of the balloon as well as the irregularities of solidified IBCA which can be seen at the level of the neck of the aneurysm are responsible for delayed thrombosis of the artery.

Considering the extent of endothelialization and the benign fibrotic tissue reaction seen, IBCA is well tolerated by the canine carotid artery. A major potential problem is the risk of embolization as a result of possible thrombogenicity of this material. In prior studies, chronic inflammatory and foreign-body reaction was seen when IBCA was injected into renal arteries, but this was not seen in our study. The IBCA injected into the renal arteries caused infarction of the tissue. It seems difficult in such cases to distinguish tissue reaction to IBCA from that caused by infarction.

Conclusions

We can summarize our results as follows:

1. Aneurysms arising from the straight portion of an artery can be obliterated with IBCA if a rigid Silastic balloon can occlude the neck of the aneurysm during the injection of IBCA.

2. A latex balloon is not stiff enough, bulges through the neck of the aneurysm, and does not prevent reflux of IBCA into the artery.

3. After 1 month, scanning electron microscopy shows epithelial cells covering the area of the aneurysm neck filled with IBCA. No inflammatory reaction is noted.

4. The Silastic balloon inflated in the artery has an angioplastic effect which causes dilatation of narrowed segments of the artery at the level of the aneurysm neck. However, the balloon induces immediate de-epithelialization in areas that are covered by new epithelial cells 1 month later.

References


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