Experimental evaluation of a tissue adhesive as an agent for the treatment of aneurysms and arteriovenous anomalies

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Studies were performed on adult mongrel dogs to evaluate the possibility of occluding saccular aneurysms and arteriovenous (AV) anomalies with an intravascular injection of the tissue adhesive isobutyl-2-cyanoacrylate (IBC). Twelve normal canine renal arteries, four surgically constructed AV fistulas, and six surgically constructed vein pouch aneurysms were occluded by the injection of IBC through a fluoroscopically positioned intra-arterial catheter. The IBC was also directly injected into 25 surgically constructed vein pouch aneurysms. Angiography performed immediately after injection and up to 3 months following treatment revealed persistent occlusion of the renal arteries, arteriovenous fistulas, and aneurysms. Tissue reaction to the IBC was mild and confined to the intima in these experiments. Further investigation of this procedure for the treatment of aneurysms and arteriovenous anomalies by either a stereotaxic or selective catheterization technique is suggested.

KEY WORDS: isobutyl-2-cyanoacrylate · intravascular tissue adhesive · experimental aneurysms · arteriovenous fistula · vascular occlusion · intracranial aneurysm

In Vitro Experiments

Method

Preliminary experiments were carried out using spherical glass model aneurysms with volumes ranging from 0.3 cc to 1.2 cc. A small hole at the neck of the aneurysm permitted introduction of a needle into the aneurysm fundus. The aneurysms were filled with citrated human blood or buffered normal saline at a pH of approximately 7.4 and both simulated pulsatile flow and temporary flow occlusion situations were tested. The IBC, supplied in glass ampules each containing 0.5 cc of the liquid, was injected using a 27 gauge needle attached to a 1 cc tubercu-
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lin syringe. The end point of aneurysm occlusion was determined visually.

Results

The IBC, when injected, rapidly polymerized to form a sponge-like mass that obliterated the aneurysm sac. The dose of the adhesive required was approximately 75% of the originally measured aneurysm volume, with the apparent discrepancy being explained by the tendency of the adhesive to trap fluid within its clefts.

In Vivo Experiments

Model

Mongrel dogs varying in weight from 6 to 34 kg and anesthetized with intravenous sodium pentobarbital were used for all experiments. The arteriovenous fistulas were created by the end-to-side anastomosis of a branch of the femoral artery to the femoral vein, while the aneurysms were constructed by a modification of the technique described by German and Black with the vein pouch being anastomosed to an elliptical opening in either the femoral or renal artery. Only those arteriovenous fistulas and aneurysms shown to be patent by angiography 1 week or more after construction were used in this study.

Method

Selective catheterization and angiography were performed by using an image intensifier with a magnetic disc recorder. The IBC was either injected through the selectively positioned catheter, or in the cases of direct injection, by a 27-gauge needle puncture of a surgically exposed aneurysm.

Angiography was performed immediately before and after treatment. Follow-up angiography was also performed at 1 week and then at monthly intervals. Animals were sacrificed at predetermined intervals to provide specimens for microscopic evaluation.

Results

Injection of Normal Canine Renal Arteries. The left renal artery in 12 animals was catheterized from the right carotid approach and 0.15 cc of the IBC injected via the catheter. When the adhesive was injected without the temporary reduction of renal blood flow (10 animals), the IBC blocked the renal artery but also embolized distally. However, the temporary proximal occlusion of the renal artery by balloon catheter during IBC injection eliminated this distal embolization. These animals provided specimens for the evaluation of the IBC-induced tissue reaction in normal arteries. Follow-up angiography up to 3 months revealed the arterial occlusions to be unchanged.

Injection of Surgically Constructed Arterio-Venous Fistulas. Under fluoroscopic control, a polyethylene catheter with an outer diameter of 0.034 inches was advanced into the fistula and 0.03 cc of IBC injected. Manual compression of the proximal femoral artery effectively reduced the fistula flow during the adhesive injection and enabled the successful occlusion of three fistulas (Fig. 1). The one failure occurred when multiple IBC injections were attempted without the temporary reduction of fistula flow; this resulted in occlusion of the fistula as well as narrowing of the femoral vein with embolic adhesive. No difficulty was encountered in removing the catheter at the completion of the procedure, and follow-up angiography up to 3 months after treatment revealed no recurrence of the fistula.

Direct Injection of Surgically Constructed Aneurysms. Twenty-five femoral artery aneurysms were surgically exposed and directly injected with the IBC through a 27-gauge needle (Fig. 2). A dose of IBC that would result in occlusion of 80% to 90% of the aneurysms was calculated from comparison of the aneurysm size on the AP angiograms with radiopaque spheres of known volume. In eight of the 20 successfully treated aneurysms, angiography after the initial IBC injection revealed incomplete aneurysm obliteration, and a repeat injection of the adhesive was performed without difficulty. Temporary proximal femoral artery occlusion was used in those aneurysms that demonstrated a rapid filling and emptying phase on pretreatment angiography. This was started after the injection of two such aneurysms without flow reduction resulted in distal parent artery narrowing secondary to embolic adhesive and qualified the results as failures. Of the three other failures, one was due to a repeat injection of what proved to be an excessive amount of IBC and the other two were due to the intentional injection of an
insufficient amount of IBC which led to dome obliteration with subtotal occlusion of the aneurysm body. Removal of the needle after completion of the injection was accomplished without difficulty, and bleeding from the puncture site was noted only when the needle was not removed immediately.

To evaluate the possibility of distal embolization occurring during direct injection, four renal artery aneurysms were constructed and treated (Fig. 3). In two aneurysms treated without the temporary reduction of blood flow, embolic adhesive was found in the kidney on microscopic evaluation. In the two aneurysms injected during a 15-second occlusion of the renal artery, satisfactory aneurysm occlusion resulted without evidence of embolization.
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Catheter Injection of Surgically Constructed Aneurysms. Six femoral artery aneurysms were catheterized from a right carotid approach (Fig. 4). Confirmation of the catheter tip position was easily accomplished by the injection of contrast media through the small selectively positioned catheter (Fig. 4 upper right). Four of the aneurysms were successfully occluded by the transcatheter injection of IBC during temporary manual compression of the proximal femoral artery to reduce blood flow. In one of the failures, a repeat injection with what proved to be an excessive amount of adhesive resulted in the occlusion of both the aneurysm and parent artery. The other failure occurred when the catheter tip migrated out of the aneurysm during femoral artery compression, and the IBC was injected into the parent artery and occluded it.

Pathological Anatomy of Specimens

Specimens of IBC Injection into Normal Renal Arteries. The polymerized IBC did not stain with hematoxylin and eosin or with orcein-van Giesen, but it was easily identified because its diffraction differs from the mounting medium. The material occluded the renal arteries at the site of injection and formed a sponge-like matrix with entrapped blood in its interstices (Fig. 5 left). The entrapped red blood cells were not hemolyzed up to 24 hours, but a faint fibrillar structure suggesting fibrin could be seen. White cells, composed of about equal numbers of neutrophilic granulocytes and mononuclear cells, tended to concentrate adjacent to the polymer at 3 hours. By 24 hours, these cells had not increased in number, and many were degenerating. At 1 week, very few erythrocytes remained in the entrapped blood, which had taken on a uniform dark eosinophilic stain. A few fibroblasts were disseminated in it, while focal groups of macrophages and granulocytes were scattered in the periphery. By 2 months, the IBC itself seemed little changed. However, the interstices were densely fibrotic, and few scattered foreign body giant cells lay adjacent to the polymer (Fig. 5 right); most surfaces of the matrix were found to be covered directly by fibrous tissue.

The reaction at the endothelial surface and in the vascular wall was of particular interest because of its relation to the problems of adhesion and toxicity. The polymer was in direct contact with only about 15% of the endothelial surface, and entrapped blood occupied the remainder. At points of contact with the wall of the artery at 3 hours, the polymer seemed to be touching the internal elastic lamina with a rare degenerating endothelial cell interposed. Often the internal elastic lamina seemed to be dented slightly outward. The media was altered only by shrinking and hyperchromatism of a few nuclei adjacent to the internal elastic lamina with no change in the adventitia. There was no progression of degeneration at 24 hours or at 3 months (Table 1).
Fig. 4. Angiograms of a femoral artery aneurysm treated by the transcatheter injection of IBC. *Upper Left:* Pre-treatment of angiogram. *Upper Right:* Angiogram after injection of contrast media through the selectively positioned catheter. *Lower Left:* Post IBC injection. *Lower Right:* Angiogram 2 months post-treatment.

Specimens after Injection into Surgically Constructed Aneurysms. The surgically constructed aneurysms as observed at 3, 6, and 12 hours after the injection of IBC had maintained their smooth muscle medial coats, and the smooth muscle cells seemed viable. Although no intima could be identified in these aneurysms after injection, neither was there any evidence of thrombosis or fibrosis. They seemed to have contained only fluid blood before injection. The IBC formed a spongy mass with entrapped blood and was attached to the wall just as in the renal artery injections. By 6 hours after injection, thrombi with lines of Zahn were formed over the IBC at the mouth of the aneurysm. These thrombi protruded into but did not occlude the parent arteries. In a specimen
examined 1 week after injection, the thrombus at the mouth was already replaced by fibrous tissue that had an endothelial surface. The organized thrombus did not intrude upon the lumen. Fibrous tissue had replaced the blood entrapped in the spongy mass near the wall of the aneurysm but had not yet reached the central portion. The smooth muscle wall of the aneurysm was degenerated, and fibrous tissue was growing through it. A fibrous capsule, about 1 mm thick, surrounded the aneurysm. Specimens at 1, 2, and 3 months had endothelial-lined fibrous walls at the mouths of the aneurysms (Fig. 6). The interstices of the IBC mass were filled with fibrous tissue containing a few scattered foreign body giant cells. The walls of the aneurysms were fibrous scars that did not extend beyond the original venous graft (Table 1).

Discussion

Earlier attempts to use a tissue adhesive as an intravascular occlusive agent were hampered by the high viscosity and slow polymerization times of the available materials. The low viscosity and rapid polymerization time of isobutyl-2-cyanoacrylate eliminates these difficulties and its apparent low histotoxicity is yet another advantage.

The treatment of arteriovenous anomalies by embolic occlusion of their feeding vessels has been hampered by the threat of aberrant embolization. The elimination of this problem by the use of selective catheterization techniques has proved difficult because
TABLE 1
The number of occluded renal arteries and occluded aneurysms autopsied and examined at various time intervals

<table>
<thead>
<tr>
<th>Time After IBC Injection</th>
<th>Specimen</th>
<th>Renal Arteries</th>
<th>Aneurysms</th>
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<tr>
<td>1 hr</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td>48 hrs</td>
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of the inability of the small catheter to transmit an embolus of effective diameter. In our studies, the IBC was injected through catheters with an outer diameter of either .020 inches or .034 inches and yet formed an occlusive mass that was apparently limited in size only by the volume injected and the temporary reduction of blood flow. Thus, the advantages of small vessel catheterization could conceivably be combined with the injection of IBC to produce a selective vascular occlusion. A similar approach to treat intracranial aneurysms will depend on advances in the field of selective intracranial catheterization that will permit safe and accurate catheterization of the aneurysm sac.

The results of the directly injected aneurysms suggest that a possible advantage of this technique in the treatment of aneurysms at craniotomy would be the minimal aneurysm exposure required to permit accurate aneurysm puncture. Should this procedure prove feasible, then stereotaxic puncture and injection of aneurysms may also be possible.

The determination of the IBC dose required to occlude the aneurysms proved difficult and resulted in the need for a reinjection in a number of animals. However, only AP angiograms were used in these calculations and the advantages of biplane angiography to aid in dose calculation are obvious. Current experiments suggest that the slow mechanical injection of IBC at a rate of 0.3 cc per min may also prevent distal embolization and eliminate the need for a reduction of blood flow through the parent artery during aneurysm injection. Should this prove true, sequential angiography performed during the aneurysm injection may allow for the accurate titration of aneurysm filling with the adhesive.

The use of vein-pouch aneurysms as an experimental model and the use of these aneurysms on the renal artery to evaluate the possibility of distal embolization appear justified. An enforced waiting period of at least 1 week between aneurysm construction and treatment admittedly reduces the number of aneurysms available for treatment, but these pouches probably more closely approximate

Fig. 6. Mouth of occluded aneurysm 2 months after injection. Fibrous tissue has surrounded the polymer and has sealed it from the lumen (L) of the parent artery. The surface of the fibrous seal has been endothelialized (arrow). H & E, ×320.
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the clinical situation than pouches produced by arterial ligation distal to a bifurcation. The limitations of this model appear to be the time involved in their manufacture, the large orifice of the aneurysm, and the frequently noted parent artery stricture at the site of aneurysm construction. However, the last two limitations may make the experimental model more advantageous since the former leads to a rapid flow situation, while the latter makes the parent artery more subject to thrombosis.

The tissue reaction of IBC in this study was mild and limited to loss of intima with minimal changes seen in the media up to 3 months following injection, while the occlusive effect of the adhesive in these experiments was satisfactory both on angiographic follow-up and microscopic evaluation. The fibroblastic invasion of the clefts within the adhesive and the endothelialized fibrous tissue bridge that crossed the neck of the aneurysms appear to indicate permanent occlusion of the structures treated.

Further experimentation with the technique, and the evaluation of long-term histotoxicity of the IBC is undoubtedly required. From the results presented, however, this appears justified and is in progress.

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References


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