In Situ $\beta$-Irradiation of a Brain Arteriovenous Malformation Model

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Background and Purpose—The treatment of large brain arteriovenous malformations (BAVMs) is challenging, and embolization alone is seldom curative. The study goal is to enhance the efficacy of arteriovenous malformation embolization by adding a $\beta$-emitting isotope to the embolic agent.

Methods—The pig rete mirabile was used as a BAVM model. The body distribution of radioactivity was evaluated after selective rete injection of $N$-butyl,2-cyanoacrylate mixed with $^{131}$I-lipiodol in 8 animals using immediate whole body $\gamma$-scintigraphy. Activities within the whole rete mirabile and selected tissue samples were quantified with a gamma counter immediately after sacrifice. Two pigs were submitted to serial $\gamma$-scintigraphies for 6 weeks to detect delayed isotope leaching. Long-term effects of in situ irradiation were evaluated using a mixture of $^{188}$Re/$N$-butyl,2-cyanoacrylate in 8 pigs. In 1 animal, autoradiography was performed to evaluate local rete mirabile distribution of the radioactivity. Seven pigs were injected with $^{188}$Re/glue in 1 rete mirabile and with glue only on the opposite side, and the degree of vascular occlusion of both sides was compared on histology at 2 (n=2) or 6 months (n=5).

Results—There was negligible activity outside the target. Radiation caused occlusion of vessels unreached by the glue itself but in the vicinity of the radioactive source in 5 of 7 rete mirabile.

Conclusions—Selective deposition of a $\beta$-emitter inside a BAVM model may be achieved by current embolization techniques. The adjunct use of an isotope may increase the efficacy of embolization. (Stroke. 2005;36:000-000.)

Key Words: arteriovenous malformation ■ embolization ■ experimental model ■ radiation therapy

Brain arteriovenous malformations (BAVMs) are congenital lesions that consist in a cluster of multiple arteriovenous shunts (the nidus). The estimated annual incidence of hemorrhage range between 2% and 4%.1 Transarterial embolization as a sole treatment of large BAVMs is seldom curative2,3 but is often used to reduce the flow and size of the lesion before surgical resection or radiation therapy.4–7 Unfortunately, concentric reduction in size is difficult to obtain by embolization and, although an important reduction of flow can be achieved, the total volume to irradiate often remains unchanged.6

We made the hypothesis that we could implant a $\beta$-emitting source into the arteriovenous malformation (AVM) nidus at the time of embolization in order to obtain an in situ irradiation. This is possible by coupling a $\beta$-emitter to current liquid embolic agents. This strategy may enhance the global reach of embolization by acting on regions of the nidus that are spared by the embolization.

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Animal Groups According to Isotope Injected and Purpose of the Study

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<th>Group</th>
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<td>Group 1 (n=8)</td>
<td>131I</td>
<td>Early distribution</td>
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<tr>
<td>Group 2 (n=2)</td>
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<tr>
<td>Group 3 (n=7)</td>
<td>188Re</td>
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CIS Bio International) is commercially available. 188Re was extracted from a 188W-188Re generator (Oak Ridge National Laboratory).9 Before extraction, the generator was rinsed with 0.9% saline solution using a volumetric perfusion pomp (Baxter Health Care). The activity of the extracted solution was measured with a radioisotopic dose calibrator (Capintec CRC-15R). The sodium perrhenate solution, obtained from the generator, was mixed with methyl ethyl ketone to ease mixing with lipiodol.

All of the angiographic procedures were done with a digitalized Siemens monoplane system. Juvenile swine weighing from 20 to 30 kg were sedated with 25 mg/kg ketamine, 1.1 mg of acepromazine, and 0.6 mg of atropine, and were then intubated after intravenous injection of 10 mg/kg methohexital and ventilated with a mixture of 2 L/min oxygen, 2 L/min nitrous oxide, and 1.5 L/min isoflurane. The right femoral artery was punctured, and the ascending pharyngeal artery was catheterized with a 5F catheter. A tracker-18 (Boston Scientific) was coaxially brought to the rete mirabile where embolization was performed under fluoroscopy.

Distribution Studies: Scintigraphy and Autoradiography

Whole body γ-scintigraphy was performed immediately after embolization with 131I using a large field-of-view γ-camera with a high energy collimator. A group of 8 pigs (group 1) was sacrificed immediately after scintigraphy, and tissue counts were obtained of the whole injected rete mirabile, as well as samples of blood, brain, kidneys, liver, lungs, and spleen. All of the organs were weighed, and activities were adjusted to estimate the total organ activity. Syringes and microcatheters were also counted after embolization.

Two other animals (group 2) were studied by serial γ-scintigraphy at 3 days and 1, 3, and 6 weeks to assess delayed leaching from the rete mirabile, and tissue counts were obtained as described above at 6 weeks.

One animal was embolized using a mixture of 0.5 mL of histoacryl and 1 mL of lipiodol-188Re (28.49 MBq/mL) and sacrificed immediately after. The rete mirabile was excised, fixed in formaldehyde, and a thick section was exposed to a high-linear sensitivity film (GafChromic, Nuclear Associates) for 234 hours. The film was read by a laser densitometer, which provides quantitative dose measurements.

Pathological Studies

In 7 animals (group 3), 1 side of the rete mirabile was embolized with the mixture of histoacryl-lipiodol and the opposite side with the same mixture with 188Re. Two animals were injected with an activity of 143.2 MBq/mL and euthanized after 2 months. Five animals were kept for 6 months before euthanized. In this group, 3 rete were injected with 360.75 MBq/mL and 2 with 58.09 MBq/mL. Sections of both sides of the rete were studied after fixation, paraffin embedding, and staining with hematoxylin phloxin safron and Mivat’s pentaichrome stain.

Dosimetry

The “dose-point-kernel” method10 was used to estimate isotope activities necessary to obtain a dose at the target in the therapeutic range of external irradiation (20 to 25 Gy). According to the known morphometric properties11 of the rete mirabile, the estimation was based on a mean artery diameter of 80 μm and a mean distance between arteries of 200 μm.

Results

Embolization could be performed in all of the animals using a technique similar to that currently used clinically for BAVM embolization.

131I

Activities in the syringe before injection varied from 95 to 222 MBq/mL. In group 1 (n=8), high activity at the target site was observed by scintigraphy in all of the animals. Although the embolic agent was restricted to the rete fluoroscopically, minimal pulmonary activity was seen in 2 of 8 animals. All of the tissues outside the rete showed either no activity or <0.6% of the activity found in their respective rete mirabile. The injected activity retained in the rete mirabile was 100% in 3 animals and ranged from 98.45% to 99.89% in the other 5 animals. In group 2 (n=2), there was no detectable activity outside the rete mirabile by scintigraphy or quantitative tissue gamma counting.

188Re

Figure 2 shows the autoradiography of the rete mirabile specimen. With the injected activity of 28.49 MBq/mL of 188Re, the dose obtained inside the embolized vessels was ≈300 cGy.

In 5 of the 7 animals, there were obvious histologic changes on the irradiated side not found on the contralateral side. These were characterized by neointimal thickening involving the arterioles that were not filled by the embolic
agent, consistent with a radiation effect from the surrounding sources. Fibrosis of the venous structures was also observed (Figure 3). Using the dose-point-kernel method, we calculated that a concentration of 277.5 MBq/mL of $^{188}$Re corresponds with a dose of 25 Gy at the target, that is, an artery unreached by the embolic agent from an embolized artery after 1 half-life.

Discussion

The treatment of BAVMs cannot be standardized, because these lesions represent a heterogeneous population with a wide spectrum of size, location, and angioarchitecture. As a general rule, surgical resection is preferred for lesions located superficially in noneloquent areas, whereas radiation therapy is indicated in small deep AVMs. The curative potential of radiation therapy is closely related to the size of the nidus, with a significant drop in efficacy for lesions $>10\, \text{mL}$. Complications also increase with lesion size. When used as a preradiosurgical treatment, embolization may significantly reduce flow but is less effective in reducing the total volume that will be submitted to radiation. The addition of a $\beta$-emitting source to the polymer used to cast the malformative nidus may enhance the efficacy of the procedure by causing obliteration of surrounding vascular channels that had escaped embolization. In our study, as shown by the quantitative autoradiography that correlated with the theoretical model (dose-point-kernel), doses similar to externally delivered doses effective for vascular occlusion in the rete could be deposited and showed actual histologic effects. However, this effect was not constant, probably because therapeutic activities could not be reached in some animals either because of lesser activity or poor penetration of the vascular structure by the embolic agent.

The porcine rete mirabile has been used for the evaluation of many embolic agents. The size of the vessels (50 to 250 $\mu$m) is similar to BAVM nidi. The rete mirabile is readily accessible to catheterization and pathologic studies. The absence of arteriovenous shunting, which compounds the problems of accurate deposition of a fluid embolic agent into the nidus, can be palliated by the surgical creation of an arteriovenous shunt. However, only 1 side of the rete is then available for embolization, whereas comparing the 2 sides was an important aspect of the present study. Because the precise control of embolic material deposition in a BAVM is difficult, the addition of an isotope raises concerns regarding exposure to the surrounding brain and also for distal organs, mainly the lungs. The low penetration of $\beta$-emitting isotopes ($<4\, \text{mm}$) is reassuring, but improving the embolization accuracy would be an important objective before using this strategy in clinical practice. More coherent liquid agents, such as EVOH (Onyx, Micro Therapeutics), could also be of value.

Figure 2. Color-coded quantitative autoradiography of a section of rete mirabile specimen after embolization of histoacryl-lipiodol labeled with $^{188}$Re (28.49 MBq/mL). Section is made in the same plane as histologic sections, that is, perpendicular to the long axis of arteries. Dose is expressed in cGy. The picture shows inhomogeneous distribution of the radioactivity because of the weak penetration of the $\beta$-ray.

Two different isotopes were used in this study. $^{131}$I was used first for practical reasons: it is commercially available in a form linked with lipiodol, which is the current opacifying agent used in conjunction with histoacryl as the embolic agent for BAVMs. Also, $^{131}$I is a dual $\beta$- and $\gamma$-emitter. The $\gamma$ component allows the use of scintigraphy for distribution mapping. However, the energy of the $\beta$-ray, ranging from 0.25 to 0.61 Mev, is too low for the appropriate penetration that is necessary for our therapeutic purposes. Thus, after the first distribution studies, we changed for a more powerful $\beta$-emitter. $^{188}$Re has a half-life of 17.01 hours. It is also a dual $\beta$- and $\gamma$-emitter with energies of 0.783 Mev and 157 Kev.

Figure 3. Histological specimen of normal rete and of both sides of an embolized rete mirabile (same animal). a, Normal rete mirabile. b, Rete mirabile side embolized with $^{188}$Re-glue. For comparison, c shows same view on the side embolized with glue only. The glue effect is a dilatation and occlusion of the artery but no effect on distant vessels. Thick arrow points to the intraluminal smooth muscle cell proliferation in a vessel that was not reached by the glue seen in a nearby vessel (thin arrow). Arrowhead shows fibrosis of the venous structures. Original magnification $\times 10$. 

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respectively. Its chemical properties allow linkage with lipiodol. With this isotope, it was possible to reach doses at the target within the range of what is expected from external radiation and observe histological effects.

The drawback of $^{188}$Re is its short half-life necessitating the use of relatively high activities that increase the risks of accidents during manipulations. $^{32}$P is an isotope that has ideal properties to overcome some of these drawbacks. Its penetration is similar to $^{188}$Re, but its half-life (14 days) is longer in the absence of $\gamma$-emission. It is, thus, more appropriate for in situ radiation therapy. Moreover, the effect of low-dose $^{32}$P on vascular occlusion and recanalization has been well documented. Future works will deal with the chemical linking of $^{32}$P to liquid embolic agents used in BAVM embolization.

Conclusion
A $\beta$-emitting source can be incorporated to the glue mixture and injected into a vascular structure using standard endovascular techniques for the treatment of BAVMs. This “radioembolization” allows the deposition of a sufficient dose to obtain expected histologic effects on vessels unreached by the embolic agent itself and, thus, could improve results of embolization treatment.

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