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Endovascular treatment of experimentally induced aneurysms in rabbits using stents: a feasibility study

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Abstract Although Guglielmi detachable coil (GDC) systems have been generally accepted for treatment of intracranial aneurysms, primary stenting of aneurysms using porous stents or implantation of coils after stent placement remains experimental. Testing of these new methods requires an animal model which imitates human aneurysms in size, configuration and neck morphology. We assessed in detail the technical requirements of and steps for transfemoral stent treatment of experimentally induced aneurysms at the top of the brachiocephalic trunk in rabbits. We created aneurysms in ten rabbits by distal ligation and intraluminal digestion of the right common carotid artery with elastase. We treated five animals with porous stents alone, and five with stents plus coiling via the meshes of the stent, which permitted dense packing of coils. No complications related to the procedures occurred. In all animals, even in those treated solely with porous stents, total occlusion of the aneurysm was achieved. Our animal model can be suitable for testing the biocompatibility and occlusion rate of new methods and devices for the treatment of experimental aneurysms.

Keywords Experimental aneurysms · Rabbit · Stenting · Guglielmi detachable coils

Introduction

Intracranial aneurysms are common, with an estimated prevalence in adults of 0.2–9% [1, 2]. They are the most common cause of subarachnoid haemorrhage (SAH), which still has high morbidity and mortality. For survivors of an acute SAH, recurrent haemorrhage from the aneurysm is a threat. The risk of rerupture is estimated at >20%, with high mortality and morbidity [3]. The two principal methods used to treat aneurysms

are surgical clipping and endovascular therapy. Since the introduction of electrolytically detachable coils by Guglielmi, they have been widely used [4, 5], especially for small-necked aneurysms. However, coil placement is often difficult in wide-necked aneurysms and associated with a high risk of coil protrusion into the parent vessel. Fusiform ectasia of vessels or giant aneurysms also pose major difficulties for the interventional neuroradiologist. Alternative endovascular treatment strategies have therefore been suggested [6, 7, 8, 9]. One approach is primary stenting of aneurysms with porous stents with subsequent coil embolisation [8, 9, 10]; other approaches include just covering the aneurysm with a porous stent [6, 11], and placing a covered stent over the aneurysm to re-establish flow in the parent vessel and close the aneurysm [12]. However, most reports of these methods in humans are anecdotal. The safety and efficacy of these methods have not been tested. Stent-related problems such as intimal hyperplasia are not well known and might seriously affect long-term results. Animal models resembling aneurysms of the cerebral arteries in humans therefore play an important part in the development and assessment of these problems.

We used a newly described and slightly modified animal model of saccular aneurysm in the rabbit, in which elastase digestion of the arterial wall of the right common carotid artery (CCA) leads to a saccular aneurysm at the top of the brachiocephalic trunk [13]. This model has considerable advantages over the swine model used for the first tests of Guglielmi detachable coils (GDC) or stents [14], in which lateral-wall aneurysms of the CCA were created surgically by arteriotomy and vein graft. The mechanical damage to the arterial wall during open microvascular surgery affects the way the vessel wall reacts to endovascular coils, since the wound changes the degree of development and intraluminal migration of fibroblasts and other cells through the disrupted basement membrane; these effects do not normally apply in human aneurysms or in our rabbit model [15]. Creating a bifurcation aneurysm at the apex of a curved artery, i.e. a terminal aneurysm, produces a situation which resembles the haemodynamic pressure and shear stress of human intracranial aneurysms more than side-wall aneurysms [16]. Endoluminal digestion of the internal elastic lamina, with spreading of elastase up to the adventitia, results in a thinner-walled aneurysm, similar to those in humans. Our purpose was to evaluate the appropriate endovascular approach and technical requirements for safe stenting of these experimental aneurysms.

Materials and methods

All experiments were performed on New Zealand White rabbits (3.5–4.2 kg) and conducted according to current German regulations and guidelines for animal welfare (AZ 50.203.2-AC 24, 24/01) and to the international principles of laboratory animal care. The aneurysms were created and subsequently treated under general anaesthesia, induced by intramuscular injection of 0.2 ml/kg ketamine (10%) and 0.3 ml/kg medetomidine, and maintained with 2.5% isoflurane inhalation. During all interventions, we gave heparin (100 units/kg) intravenously.

Aneurysms were constructed in ten animals employing a method previously described [13] but slightly modified by our group [17]. In short, the right CCA was surgically isolated, ligated distally and controlled proximally with 3-0 silk sutures before a 1–2 mm bevelled arteriotomy was made and a 4F vascular sheath was passed retrogradely to the midportion of the CCA. Under fluoroscopic guidance, a 2F Fogarty balloon was passed retrogradely to the origin of the CCA and, once in position, inflated with iodinated contrast medium. Occlusion of the vessel was verified by retrograde injection of contrast medium via the sheath. If we saw collaterals to the trachea or aberrant muscular branches originating from the CCA, the sheath was placed further proximally towards the origin of the CCA to avoid elastase leakage through these vessels which might result in tracheal necrosis. We then advanced a microcatheter supported by a microguidewire through the same sheath, and under fluoroscopic guidance placed the microcatheter directly distal to the Fogarty balloon.

Porcine elastase was mixed with nonionic contrast medium to obtain a 50% dilution. We administered 20 units of elastase and left it within the isolated right CCA for 20 min, after which the balloon was deflated, the sheath removed and the vessel ligated in its midportion. The skin was closed with a running suture. Aneurysms formed from the stump of the right CCA.

Endovascular treatment was carried out via a right transfemoral approach 2–3 weeks after creation of the aneurysm. The right common femoral artery was exposed and ligated distally. After performing a 1–2 mm bevelled arteriotomy, we passed a 4F sheath retrogradely over a 0.018 inch guidewire. A microcatheter was introduced over a microguidewire through the sheath into the artery, without using a guiding catheter, and directed along the right iliac artery and up to the aortic arch. Using the microguidewire, the microcatheter was advanced into the brachiocephalic trunk. After removing the microguidewire, we performed digital subtraction angiography (DSA) through the microcatheter, with not more than 1.5 ml contrast medium per injection. The size of the aneurysm was determined in relation to an external sizing device which was in place during the diagnostic angiography. Using fluoroscopy and "road-mapping", an oversized exchange microguidewire was passed through the microcatheter and placed distally into the subclavian artery. Over this wire we passed the stent

(Aachen Resonance Flex Force balloon-mounted stent 4 mm diameter, 12 mm long, Aachen, Germany) mounted on a balloon catheter into the brachiocephalic trunk. Using the microcatheter we then performed a new roadmap with the stent in place but uninflated to allow for possible slight modification of vessel anatomy due to the balloon catheter. We then inflated the balloon using iodinated contrast medium and thereby deployed the stent over the aneurysm neck. The balloon catheter was removed, leaving the stent in place.

In five animals we then performed DSA of the brachiocephalic trunk through the microcatheter; in the other five we directed the microwire followed by the microcatheter, through the meshes of the stent into the aneurysm and delivered soft coils into the aneurysm via the microcatheter under continuous fluoroscopic control, using the roadmap technique. Depending on the size of the aneurysm, the diameter and length of the first coil were from 6 mm and 15 cm, respectively, down to 2 mm and 2 cm. Tight packing of the aneurysm was achieved by using progressively smaller coils. After the procedure, we performed DSA of the aneurysm-bearing brachiocephalic trunk through the microcatheter. Thereafter the catheter and sheath were removed, the femoral artery ligated with a 3.0 silk suture and the skin closed with a running suture.

Results

All rabbits tolerated the surgical and endovascular treatment procedures well. The aneurysms resembled those on human cerebral arteries in size, configuration and neck morphology [18]. It was possible to place the uncovered stents in the parent artery, i.e. the brachiocephalic and subclavian arteries, preserving both the right vertebral artery and left CCA, which typically emerges from the base of the brachiocephalic trunk in rabbits. Anchoring the stent in the parent artery at either end of the neck of the aneurysm resulted in satisfactory expansion of the device, despite the lack of vessel wall apposition at the neck.

We were able to enter the lumen of the aneurysm with the microcatheter through the mesh of the stent in all rabbits, and to deliver the coils successfully, with dense packing of the aneurysm in every case. All coils could be placed outside the stent, within the aneurysm; no loop protruded via the mesh and the coil mass did not impinge on the parent artery.

Postembolisation DSA revealed complete occlusion of all aneurysms in the two groups, with no contrast medium visible within the aneurysm. However, in two animals treated simply by stent placement a faint blush was visible at the site of the aneurysm, presumably reflecting contrast medium still entering the partially thrombosed aneurysm. After approximately 5 min, no blush was observed in either animal. There were no complications such as haemorrhage, thrombosis, coil dislocation or rupture of an aneurysm.

Discussion

The aneurysm model we employed has been described in great detail from the viewpoint of aneurysm creation [13, 15]. Reports on how to place coils within the aneurysm have also been published [19, 20]. This is the first study to demonstrate the efficacy and feasibility of using this model to place stents over the aneurysm and to coil the aneurysm successfully via the meshes of the stent. Our goal was not to make short- or long-term observations on these experimentally induced aneurysms at the apex of the brachiocephalic artery treated with the methods described, but to demonstrate the procedural and technical requirements for their practicable endovascular treatment. Further studies on the histological findings and time-dependent changes in the treated aneurysms will follow.

During intracranial stent placement, the most prominent obstacle is tortuosity of the vessels such as the carotid siphon. Entering these vessels with an rigid balloon catheter almost invariably generates vasospasm. Another problem is stenting over small, angiographically invisible, perforating arteries which should remain patent [7]. In our model both the tortuosity of the vessels and the presence of perforating arteries were simulated. We had to navigate the balloon catheter across the aortic arch into the brachiocephalic artery, around two rather narrow curves, to reach the point of stent deployment; this was possible in all ten animals. In almost all cases the stent covered either the left carotid artery or the right vertebral artery as well as the neck of the aneurysm. Both arteries remained patent on immediate follow-up angiography. Since, after establishment of the aneurysm, the animals rely solely on supply from the left CCA, even delayed occlusion of this vessel should have resulted in severe neurological deficits or death, which did not occur in our experimental setting. However, the histological examinations on these animals remain to be done to assess intimal proliferation, especially at the margins of the stent.

We found complete angiographic obliteration of the aneurysm immediately after stent placement, without coiling. Geremia and colleagues [6, 11] found in experimentally created aneurysms, both fusiform and side-wall, similar results which remained stable over 8 weeks. They attributed this complete obliteration to changing haemodynamics within the aneurysm and subsequent thrombus formation. Stent placement promotes stasis within the residual lumen between the stent wall and the outer wall of the aneurysm, presumably because the wire mesh interferes with the

usual blood flow pattern, producing thrombus and even fibrosis within the residual aneurysm lumen. We have not yet conducted follow-up examinations of these aneurysms but found initially the same results with a widely patent parent artery and no contrast medium entering the aneurysm. However, our aneurysm model more closely resembles that in humans: we did not produce side-wall aneurysms which are more prone to spontaneous thrombosis than our bifurcation aneurysms. It therefore remains to be seen whether our aneurysms also remain occluded.

Simple stent placement over aneurysms, especially those with a wide neck, therefore, needs refinement which may help to ensure occlusion. The combination of coiling and stenting has been described in recent case reports and an animal study. The stent across the neck of the aneurysm can act as a barrier through large coil baskets can be delivered without the danger of loops protruding and through which, at the end of the session, smaller coils can be deposited near the neck without the risk of migration [21]. This technique thus helps achieve more complete occlusion, especially of wide-necked aneurysms, without remnants. We found it possible in all cases to enter the aneurysm with the microcatheter after stent placement and to deliver coils within the thus protected aneurysm. The model is, therefore, not only suitable for teaching neuroradiologists in training the techniques of coiling over a stent and how to enter an aneurysm through its meshes, but can also be used to test new coil materials in conjunction with protective stents. The tortuosity of the vessels does not make this intervention straightforward, but it more closely resembles the situation in patients, with difficulties of access to the lumen of the aneurysm.

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