Radioactive Coil Embolisation of Intracranial Aneurysms

Experimental and Preliminary Clinical Data

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Introduction

Coil embolisation of intracranial aneurysms can improve the outcome of patients treated after subarachnoid haemorrhage as compared to surgical clipping¹. Unfortunately, angiographic recurrences are not infrequent and although their clinical significance remains to be determined, they may be responsible for future ruptures². In situ beta radiation, using coils ion-implanted with ³²P, may prevent recanalization and thus improve long-term results of endovascular treatment.

The present article will review the experimental data as well as present the clinical feasibility of radioactive coil embolisation of intracranial aneurysms.

Material and Methods

Ion Implantation of Coils

³²P-coils were produced as previously described³ on a dedicated radioactive ion implanter at the Université de Montréal. ³²P was purchased from Perkin Elmer Life Sciences. Coils, a kind gift from Target Therapeutics (Fremont, California), were measured after implantation, identified, sterilized, and inserted into Plexiglas boxes. The typical radioactive coil kit consisted of 20-30 platinum coils, 14 to 2 mm in diameter, of calibre 0.015 for sizes 5 mm and

above, and of calibre 0.010 for smaller coils, ion-implanted with 0.13-0.26 μ Ci/cm.

Endovascular Interventions

Bifurcation aneurysm model and the single coil arterial occlusion model have been previously described³. The technique for endovascular treatment with platinum coils was exactly as previously described except that radioactive instead of standard coils were used.

During clinical interventions, physicians (JR, DR, AW, FG) could always choose a non-radioactive coil from the inventory, if they felt it would be safer, more effective, or more appropriate for each coil deposition. All procedures were performed under general anaesthesia, with systemic heparinization and using a monoplane c-arm angiographic system without 3D-reconstruction. Personnel involved in the procedure were trained by the radiation safety officer in the appropriate handling of ³²P. There was no additional measure to the standard precautions in the handling of material in contact with body fluids that in effect also minimize risks of radioactive contamination.

Calculation of Therapeutic Activities

Aneurysm dimensions were estimated using the first coil as a reference. The volume of aneurysms was calculated according to an ellipsoid model⁴. In cases already presenting a re-

Figure 1 *Animal model.* Macro (A,B) and microphotographs (C,D) of axial sections of canine maxillary arteries occluded with 3 mm x 10 cm radioactive (1.4 μCi in B,D) or non-radioactive coils. Macrophotographs (E,F) of the neck of canine bifurcation aneurysm 3 months after embolization with radioactive (F) or non-radioactive (E) coils. Please note complete recanalization in A,C, while arteries occluded with the radioactive coil are fibrosed, and thick neointima at the level of the neck of aneurysms treated with radioactive coils.

currence, the volume was limited to the opacified portion of the aneurysmal sac. The target therapeutic activities to be introduced into each lesion was calculated using the formula:

Target activity = $0.018 \mu\text{Ci} \times \text{volume of aneurysm in mm}^3$ ⁴.

Local injection of colloidal ^{32}P have been used for many years to prevent recurrences after stereotactic aspiration of cystic craniopharyngiomas⁵. We have fixed maximal activities per volume according to tables used for years in this form of treatment. Dose-point kernel methods and Monte Carlo simulations were performed to calculate the dose to surrounding tissues when the target volumetric activities ($0.018 \mu\text{Ci} \times \text{mm}^3$) are reached as well as effective doses in patients included in the pilot study.

Retrospective Clinical Studies

We studied the total length of coils deployed into 357 intracranial aneurysms. Aneurysmal volumes were estimated using 3 mathematical

models. We simulated that coils were implanted with $0.26 \mu\text{Ci/cm}$ of ^{32}P , calculated resulting volumetric activities and compared them to "effective" levels derived from experimental data and "safe" levels prescribed for the clinical use of ^{32}P in cystic craniopharyngiomas⁶.

Results

Experimental Evidence in Canine Arteries and Aneurysms

Coil embolisation is routinely followed by recanalization in canine arterial models. Local beta radiation emitted from ^{32}P ion-implanted platinum coils reliably inhibited this recanalization process³. The efficacy of inhibition of recanalization was dependent on coil activities, reaching more than 85% when coils were implanted with $0.13 \mu\text{Ci/cm}$ of ^{32}P or above. In further experimental studies, using various combinations of coils and stents ion-implanted with various linear and total activities, recanalization could be inhibited with efficacy as long as activities per volume of target arteries were $0.018 \mu\text{Ci/mm}^3$ or above⁷. Experimental bifurcation aneurysms embolised with radioactive coils did not recanalize, while aneurysms treated with control coils showed recanalization and recurrences at 12 weeks³. The neointima formed at the surface of the coil mass at the neck of experimental aneurysms was thicker and more complete than the one found at the surface of standard coils³.

Simulations Using Retrospective Data

A simulation of radioactive coil embolisation of human aneurysms, using a retrospective study of the length of coils introduced into 357 consecutive patients treated with platinum coils, showed that reaching the target activity of $0.018 \mu\text{Ci/mm}^3$ would be feasible in at least 92% of patients, had the coils been implanted with $0.26 \mu\text{Ci}$ of ^{32}P per cm^4 . This level of activities may become difficult to reach in large aneurysms in which packing densities tend to be lower, and which may necessitate the use of coils ion-implanted with higher linear activities of ^{32}P .

Dosimetry

Dose-point kernel methods and Monte Carlo simulations showed that doses to tissues delivered by coils when the target activity is

Figure 2 Dosimetry of a ^{32}P coil in the arterial model. Graph showing theoretical lifetime dose to tissues of a 3 mm x 10 cm platinum coil ion implanted with a 0.13 $\mu\text{Ci}/\text{cm}$ of ^{32}P and used to embolize a 3 mm maxillary artery according to the dose point kernel method.

reached are well below those obtained for the treatment of cystic craniopharyngiomas. They can reach 10 Gy to a 3 mm ring of tissues surrounding the aneurysm only in large lesions above 20 mm. In the preliminary clinical study, mean doses for the lifetime of the isotope to a 3 mm rim surrounding the lumen of aneurysms was 16.2 Gy. These calculations did not take into account the shielding effects of platinum coils within the lesion, the presence of partial thrombosis or of a cap of compacted coils in lesion treated for recurrences and the correction factor for beta radiation.

Preliminary Clinical Study

During a first phase of a feasibility trial, patients (n=12) were selected because:

1/ Aneurysms were considered unsuitable for surgical treatment and 2/ they had already recurred after endovascular treatment or 3/ they presented lesions with characteristics associated with a high risk for recurrence (large and giant aneurysms or wide-neck aneurysms (>4 mm)). Inclusion criteria were then widened to include any patients considered for endovascular treatment.

There were 41 patients, 34 to 84 year old, for a mean of 57 ± 14 . Most patients (80.5%) were women. They were treated electively (59%) or during the acute phase after subarachnoid haemorrhage (42%). Most patients (38/41) were treated for one lesion, while 3 patients had 2 aneurysms treated with radioactive coils. Aneurysms (n=44) were most frequently basi-

Figure 3 Radioactive coil embolization of basilar aneurysm. Postero-anterior views from vertebral angiography performed A) before B) immediately and C) 6 months after embolization of a wide-necked basilar bifurcation aneurysm with radioactive coils; a total of 10.3 μCi of ^{32}P were inserted into the aneurysm.

lar bifurcation (34%), posterior communicating (16%), ophthalmic carotid (14%) and anterior communicating artery aneurysms (11%). Lesions were 4 to 30 mm in size (mean 10.4 mm $\pm$ 5.8), with a mean neck diameter of 4.7 mm $\pm$ 1.7. Five lesions (11%) were giant (>25 mm). In twelve cases (27%) the lesion was already a recurrence following 1 to 4 endovascular procedures.

Most lesions (43/44; 98%) had at least one risk factor for recurrence (previously identified and published²).

Forty of forty-four aneurysms (91%) could be treated with radioactive coils. Initial angiographic results were satisfactory (complete occlusions or residual necks) in 75% of lesions. The target activities could be reached in 88% of lesions that could actually be coiled (35/40), and maximal activities were never exceeded. Total activities ranged from 1.72 to 80.0 mCi for a mean of 20.13 μ Ci $\pm$ 20.80. Volumetric activities ranged from 0.01 to 0.17 μ Ci/mm³ for a mean of 0.06 $\pm$ 0.04 μ Ci/mm³. Activities for each lesion plotted according to target and maximal values are illustrated in figure 1. Lesions were treated with a mean of 107 $\pm$ 109 cm (range 8-466 cm) of radioactive and 48 $\pm$ 64 cm (range 2-210 cm) of non-radioactive coils. The mean packing density was 25 $\pm$ 17%.

Rebleeding was prevented in all 18 patients with subarachnoid haemorrhage.

Thromboembolic complications occurred in 3 patients (7%). In 2 patients these complications were asymptomatic, but one patient suffered cerebellar and thalamic infarctions from deliberate occlusion of the posterior cerebral and superior cerebellar arteries in attempting to treat a giant aneurysm (patient 2; GOS IV). Overall 35 (85%) of patients had a good outcome (32 GOS I and 3 GOS II). Six patients (15%) had a bad outcome (4 GOS III, 1 GOS IV and 1 GOS V). In seven of a total of nine patients with neurological deficits, these were sequelae from the initial subarachnoid haemorrhage or subsequent disease-related complications such as vasospasm (2 GOS II, 4 GOS III).

One patient presented 5 months after incomplete occlusion of a complex posterior communicating artery aneurysm with subarachnoid haemorrhage (Hunt & Hess grade II). Follow-up angiography showed a minor recurrence. The lesion was treated by surgical clipping with a good outcome (GOS II).

Angiographic follow-up studies at 6-12 months are available in 37 lesions including 36 or 90% of those actually treated with radioactive coils. Results were stable in 25 (69%) of lesions. Recurrences (of any type) were found in 11 (31%), including 5 major recurrences (14%). According to our previous retrospective study (2), the characteristics of lesions and the length of angiographic follow-up periods, we should have expected 16 recurrences, including 6 major ones.

There was no complication related to beta radiation during a mean follow-up of 10 months (range 6-22). One year follow-up imaging studies (MRI and CT-Scan) have yet to be performed in most patients.

Discussion

In situ beta radiation is a new strategy designed to prevent recanalization after endovascular treatment¹. Although exact mechanisms responsible for this effect of radiation remain to be determined, we believe this phenomenon should be exploited to decrease recurrences after endovascular treatment of intracranial aneurysms.

Because beta particles emitted from ³²P have a limited penetration (70% of the energy is deposited within 1 mm), this strategy limits radiation exposure to tissues in the immediate vicinity of coils. Since ion-implantation renders platinum coils radioactive without any mechanical alteration of the device³, endovascular treatment can be performed with the same security as the current treatment and using the expertise interventionists have developed over the past 10 years.

The animal studies have clearly demonstrated the strength of the recanalization process in normal arteries. Beta radiation is the only strategy that has shown efficacy in the prevention of recanalization after coil occlusion in animal models^{3,4}.

To ensure the same safety and efficacy as standard coil interventions, a combination of standard and radioactive coils may be appropriate in many instances. Thus linear activities must be converted into volumetric activities to assess if sufficient activities have been introduced into clinical aneurysms. Retrospective simulation studies have shown that, had the coils been ion-implanted with 0.26 μ Ci/cm, 92-

98% of 357 lesions would have reached "effective" therapeutic levels according to preclinical data.

The feasibility of the radioactive coil strategy was truly tested in the preliminary clinical study; it was possible to reach target activities in more than 80% of lesions without exceeding arbitrarily fixed maximal values.

This initial experience included many large and giant aneurysms, those requiring the widest variety and the largest number of coils per lesion. The fact that we could effectively reach the target total activity for most lesions is encouraging.

A second goal of the pilot study was to verify that there would be no added complication related to radiation. Although radioactive coil embolisation is a new treatment, small activities, low penetration of beta radiation, short half-life, low-dose rate and the fact that we have fixed maximum activities corresponding to therapeutic activities per volume classically used in the treatment of benign intracranial cysts will assure that radiation injury to neighbouring structures will be minimal or absent. A valuable safety study is however beyond the scope of this pilot study and would need to be integrated into a large-scale efficacy study with longer follow-up periods.

The preliminary clinical study was not designed to assess efficacy: Total numbers are small, confidence intervals are wide, and recurrence rates that were observed are compatible with any hypothesis (success or failure in decreasing recurrences). Other strategies have re-

cently been proposed to improve long-term results of coil embolisation^{8,9}. Unfortunately, the regulatory pathway that has been chosen to introduce these coils in clinical use is one of equivalence with the previous standard platinum coils and clinical studies have not been planned to test for efficacy. With the future availability of multiple potential alternative embolic agents with unproven clinical efficacy, indications for each agent may not be supported by scientific data. Only a randomized study on a total of 500 patients (250 in each group, including acutely ruptured lesions in patients that may not survive to contribute to the primary endpoint) could verify if a new generation coil, including radioactive coils, could diminish angiographic recurrences, from an expected rate of 20% in the control group treated with standard coils, to 10%, with an α -error of 5% and a β -error of 20%.

Conclusions

In situ beta radiation can prevent recanalization after coil embolisation in animal models. Radioactive coil embolisation is feasible. A randomized study comparing radioactive and non-radioactive embolisation of aneurysms is necessary to assess if beta radiation can improve long-term results of endovascular treatment of aneurysms.

Acknowledgments

We acknowledge the financial support from the Canadian Institutes of Health Research, Canadian Heart and Stroke Foundation, Valorisation Recherche Québec and the Natural Sciences and Engineering Research Council of Canada.

References

- 1 Molyneux A, Kerr R et Al: International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 360 (9342): 1267-1274, 2002.
- 2 Raymond J, Guilbert F et Al: Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke* 34: 1398-1403, 2003.
- 3 Raymond J, Leblanc P et Al: In situ beta radiation to prevent recanalization after coil embolisation of cerebral aneurysms. *Stroke* 33: 421-427, 2002.
- 4 Raymond J, Leblanc P et Al: Feasibility of radioactive embolisation of intracranial aneurysms using 32P-implanted coils. *Stroke* 34: 1035-1037, 2003.
- 5 Janicki C, Seuntjens J: Evaluation of the dose to cyst wall and to surrounding tissues in P-32 and Y-90 radio-colloid treatments of cysts using the dose-point-kernel and Monte-Carlo methods. *Med Phys* 29: 1203, 2002.
- 6 Shapiro B, Fig LM, Gross MD: Intracavitary therapy of craniopharyngiomas. *Q J Nucl Med* 43: 367-374, 1999.
- 7 Raymond J, Leblanc P et Al: Beta radiation and inhibition of recanalization after coil embolisation of canine arteries and experimental aneurysms: how should radiation be delivered? *Stroke* 34: 1262-1268, 2003.
- 8 Kallmes DF, Fujiwara NH: New expandable hydrogel-platinum coil hybrid device for aneurysm embolisation. *Am J Neuroradiol* 23: 1580-1588, 2002.
- 9 Murayama Y, Vinuela F et Al: Bioabsorbable polymeric material coils for embolisation of intracranial aneurysms: a preliminary experimental study. *J Neurosurg* 94: 454-463, 2001.

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