Endovascular Treatment of Experimental Cerebral Aneurysms Using Thermoreversible Liquid Embolic Agents

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Summary

We have developed a new embolic agent, thermoreversible gelation polymer (TGP). This polymer is unique in that solidification occurs at body temperature. The utility of this new liquid embolic agent for the treatment of large experimental aneurysms was evaluated angiographically.

TGP remains liquid at temperatures below the sol-gel transition temperature (TT) and becomes gelatinous above the TT. TGP can also be used to slowly deliver biologically active substances such as growth factors or engineered cells. In this study, TGP was mixed with radiopaque material without solvent. Bilateral common carotid arteries of swine (n=5) were used for surgical creation of lateral aneurysms, then 1 aneurysm in each animal was embolized using TGP without any protection device. The remaining untreated aneurysm in each animal was used as a control.

All aneurysms were successfully embolized using TGP. No distal migration of TGP was observed when aneurysms were embolized without using protection devices.

TGP can be safely used to embolize experimental aneurysms. Embolization of aneurysms with a protection device needs to be evaluated. Further modifications such as mechanical stability and use as a drug delivery system will be necessary prior to the clinical application of TGP.

Introduction

Endovascular therapy has recently been used for treating cerebral aneurysms¹³. Over the past decade, endovascular therapy using Guglielmi detachable coils (GDCs) has been shown to represent a successful alternative for the treatment of intracranial aneurysms. The major weakness of the GDC system is the possibility of aneurysm recanalization, particularly in wide-necked or large/giant aneurysms.⁶ Liquid embolic agents can increase the rate of occlusion, irrespective of the form of aneurysm. Some experimental liquid embolic agents have been developed^{2,7-12,18-23}. Onyx (Micro Therapeutics, Irvine CA) is currently the most widely used liquid embolic agent. Application of this material to the treatment of intracranial aneurysms has been developed following experimental work¹⁸. The Onyx system comprises a liquid embolic agent developed for endovascular use, as reported in the Cerebral Aneurysm Multicenter European Onyx (CAMEO) trial¹⁴. This technique offers relatively poor control of migration of the liquid embolic agent into the parent artery.

We have developed a thermoreversible gelation polymer (TGP) (figure 1)²⁶⁻²⁸. TGP is a gelatinous solid at temperatures above the sol-gel transition temperature (TT; 20 °C), and liquid below the TT. This polymer is unique in that solidification occurs immediately at physiological temperatures. The aim of this study was to

Figure 1 When injected into hot water, TGP solidifies like a coil.

evaluate feasibility for injecting TGP as a liquid embolic agent into an experimental aneurysm.

Methods

The study was conducted according to the standard operating procedures of our animal research committee. Swine (n=5) were acclimated to laboratory conditions for ≥ 7 days before aneurysm construction and embolization. Animals were approximately three to four months-old and weighed 20-25 kg.

TGP Preparation

TGP (MB-10 gel; Mebiol Inc, Hiratsuka, Japan) is supplied as a lyophilized, sterilized polymer (1 g) within a cell culture flask (25 cm²). For the present study, 1 g of TGP was dissolved in 9 g of sterilized saline under refrigerated conditions (4 °C) at a concentration of ten wt %. To achieve appropriate radio-opacity, autoclaved tantalum powder (3.6 g) was suspended in 10 wt % TGP gel solution (8.4 g) in an ice bath and drawn up in a 1-mL disposable syringe (figure 2). All procedures were performed under sterile conditions and TGP was stored as a gel in a refrigerator at above 20 °C.

Aneurysm Construction

Experimental lateral wall aneurysms were constructed in bilateral common carotid arteries in 5 animals using microsurgical technique. The technique of aneurysm construction has been reported previously¹⁷. The two aneurysms con-

structed in each animal were similar in diameter (8-30 mm) and neck size (≥ 5 mm) (figure 3).

TGP Injection

A 6-F sheath was placed in the right femoral artery after standard Seldinger puncture and catheterization. Selective common carotid arteriography was performed using a 5-F long taper diagnostic catheter (Terumo, Tokyo, Japan). Aneurysms were shown in angiographic orthogonal projections. An intravenous bolus of 3000 U of heparin was injected to prevent thromboembolic complications.

A diagnostic catheter was introduced into the aneurysm and continuously flushed with cold saline (4 °C). TGP was then injected into the aneurysm under hypothermic conditions using a 1-mL disposable syringe. Animals underwent embolization of the right-side aneurysm using TGP, while the left-side aneurysm was left unembolized as a control. Blood flows in the parent artery and left-side control aneurysm were examined angiographically at 0, 3 and 6 h after

Figure 2 TGP in a 1-mL disposable syringe (Medallion Syringe)

embolization of the right-side aneurysm.

Results

TGP was easily injected using a 1-ml syringe. All aneurysms were successfully embolized by TGP. In each case, almost the entire aneurysm was completely embolized (figure 4). Angiography at 0, 3 and 6 h after embolization showed no evidence of recanalization (table 1). Left-side control aneurysms displayed no thrombus at 0, 3 and 6 hours after embolization of the right-side aneurysm. TGP solidified rapidly after leaving the catheter. However, injection was prevented if the catheter was warmed by the blood beyond this time, causing solidification of the TGP.

Discussion

Limitations of GDC Embolization

Endovascular treatment of cerebral aneurysms has become a valid alternative to conventional neurological clipping. GDCs were introduced 1990 for the occlusion of cerebral aneurysms using an endovascular approach^{4,5}. The advent of GDCs provided a safe and effective treatment for a large population of cerebral aneurysms^{1,3,6,13,15,16,24,25}. However, various anatomical limitations to the use of GDCs in treating aneurysms have been identified, and GDCs have been shown to be less effective in wide-necked or large/giant aneurysms. In these types of aneurysm, achieving complete packing and control of aneurysm inflow is difficult using GDC technology, and coil compaction and recanalization may occur.

Advantages and Limitations of Liquid Embolic Materials

Liquid embolic materials represent one possible alternative for the treatment of some cerebral aneurysms. Such materials can be used to embolize wide-necked or large/giant aneurysms^{2,7-9,11,12,18,20-23}. However, the technique has not been universally accepted, due to the intrinsic technical limitations¹⁸. We have developed TGP as an improved liquid embolic material. It was originally developed as a tissue engineering

Figure 3 Pre-embolization angiography. Side-wall aneurysm in a porcine model.

Figure 4 Postembolization angiography. Aneurysm is almost completely embolized. Left: digital subtraction angiography; Right: digital angiography.

cell culture material. Therefore potentially it can be used as drug or cell delivery vehicle.

Angiography performed immediately after embolization showed complete occlusion in all animals in the present study. TGP was successfully injected in a liquid state using a catheter.

The problem of liquid embolic materials such as Onyx is that the technique is irreversible and potential toxicity due to solvent. TGP, however, is a thermoreversible polymer without solvent. Thromboembolic complications may occur when any liquid embolic material migrates from an aneurysm into the parent artery, whereas migrated TGP can be re-liquefied simply by exposure to a suitably low temperature. Once it was re-liquefied no solidification was observed due to low concentration of the polymer. In this study we only evaluate acute performance of this new material. Long-term evaluation and histological studies are needed. Another limitation of this study was delivery system. In this feasibility study we did not use microcatheter system because of difficulty of injection due to solidification during delivery. Appropriate cooling system is underdevelopment.

Table 1 Follow-up angiography for embolized aneurysms.

n°	Immediately	After 3 hours	After 6 hours
1	complete occlusion	not recanalized	not recanalized
2	complete occlusion	not recanalized	not recanalized
3	complete occlusion	not recanalized	not recanalized
4	complete occlusion	not recanalized	not recanalized
5	complete occlusion	not recanalized	not recanalized

Conclusions

We successfully embolized experimentally produced wide-necked lateral wall aneurysms using TGP, a novel embolic agent. Long-term and

pathological evaluations are necessary. By taking advantage of the features of this polymer, such as the capacity to deliver drugs or cultured cells, TGP may also prove useful for the treatment of AV malformations, AV fistulas and tumors.

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