In vitro and in vivo evaluation of chitosan-sotradecol hydrogel, an embolizing sclerosing agent for the treatment of endoleaks

Fatemeh Zehtabi [1, 2], Ahmed Fatimi [1,2], Antony Bertrand-Grenier[2] , Gille Soulez[2,3], Sophie Lerouge[1,2]
1. Laboratory of Endovascular Biomaterials (LBeV), École de technologie supérieure (ETS) /
2. CHUM Research Center (CRCHUM), Montréal, QC, Canada.
3. Department of Radiology, Hospital of the University of Montreal (CHUM), Montreal, Quebec, Canada

Introduction: Endovascular aneurysm repair (EVAR) of abdominal aortic aneurysms (AAAs) with a stent-graft (SG) is limited by the persistence of blood flow perfusing the aneurysm, called endoleaks. Sac embolization has potential to minimize or prevent endoleak, but presently commercialised embolizing materials have several drawbacks and do not fully prevent endoleak, therefore there is a clear need for a new more efficient embolizing agent. Previously, our team showed that the endothelial lining, a thin layer of cells that lines the interior surface of blood vessels, has an important role in endoleak persistence and recurrence [1]. Therefore in order to combine blood flow occlusion and endothelium ablation properties, an injectable radiopaque hydrogel based on the combination of chitosan–β-glycerophosphate thermogels with a radiopaque agent and sodium tetradecyl sulfate (STS), a sclerosing agent commonly used in sclerotherapy, was developed [2]. The aim of the present study was to demonstrate the advantage of such an embolizing sclerosing agent (CH-STS) compared with an embolizing but non sclerosing agent (CH) to prevent endoleaks and to further evaluate of its benefit and possible drawbacks. Thus our approach consisted in comparing CH-STS with CH gels of similar mechanical properties in the same animal, using a bilateral iliac aneurysm model already validated by our team. This was preceeded by the *in vitro* study of the rheological behavior, radiopacity, morphology, injectability and ability to occlude blood flow, using *in vitro* bench tests.

Methods: CH-STS and CH gels were prepared by mixing a) a solution of CH (DDA= 94%) dissolved in acidic solution containing contrast agent (iodixanol from GE Healthcare, USA) and b) a solution containing BGP (Sigma) with or without STS (sigma). The gelation kinetic of gels as a function of time at fixed temperature (37°C) was studied by rheology on a Physica MCR301 (Anton Paar). Injectability and efficiency to occlude blood flow were evaluated on custom-made *in vitro* bench tests. In brief, injectabiliy was assessed by measuring the force needed to inject the gel through a lumen catheter with internal diameter of 0.61 mm (0.024 inch) and absence of damage observed in rheological properties. Occlusive properties are defined as the maximal pressure sustained by the gel submitted to a liquid of similar viscosity than blood. A bilateral aneurysm model was used for *in vivo* evaluation [2]. In 12 dogs, one aneurysm was injected with CH-STS hydrogel while the contralateral side was injected with CH, with follow-up imaging by US, angiography and CT scan at sacrifice [2]. Three or six months after embolization the animals were killed and serial transverse sections of the aneurysms were performed for macroscopic observation and histology.

Results: The two formulations tested immediately formed gels with physiological pH at body temperature. In vitro embolization tests showed that even though the CH-STS exhibited higher rheological properties, both gels are cohesive enough to rapidly occlude blood flow at pressures up to 200 mmHg. Injectability was possible even several minutes (up to one hour) after mixing the two solutions, with no drastic increase of the force required, which means that the risk of catheter occlusion or catheter sticking into the artery is low. Based on the *In vivo* results, summarized in Table 1, CH-STS gels led to fewer endoleaks occurrence and no adverse effect such as SG thrombosis.

Table 1: Summary of endoleak and SG thrombosis in both groups

	CH-STS	CH
Endoleaks	4/12	9/12
Endoleak ''recurrence''	1	3
SG thrombosis *	0/12	1/12

In the case of CH-STS gels, the main source of recurrence of endoleak was incomplete initial embolization. Whereas, for CH gels endoleak recurrence were observed in the peripheral portion of the aneurysm and often (Fig.1) by the presence of recanalized channels through the chitosan matrix (Fig.2). After 3 and 6 months, most of the hydrogel was still visible inside the aneurysm, with strong inflammation reaction around the hydrogel.

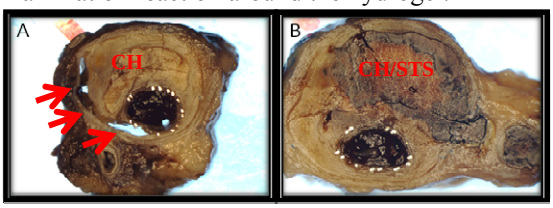

Fig.1. Macroscopic pictures of aneurysm treated by a) CH and b) CH-STS gels in the same animal (Leak is shown with arrows)

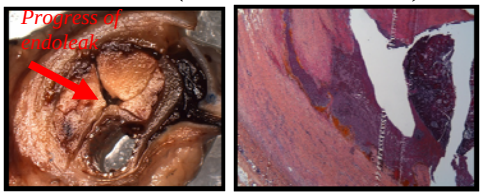

Fig.2. One example of Microscopy and HPS staining pictures of presence of endoleak throughout the CH gels

Conclusion: Obtained results of animal study suggest that in comparison with CH, CH-STS are less prone to endoleak recurrence and persistence.

References: 1. G.Soulez, et al., journal of Vascular and Interventional Radiology, 2008. vol. 19, pp. 1070-8 **2**. A. Fatimi, et al., Acta Biomater, 2012. p. 2712–2721.
Funding: CIHR POP and Canada research chair program. Thanks to H. Héon for her assistance in animal experimentation.