Embolization of abdominal aortic aneurysm using a radio-opaque hydrogel combining embolic-sclerotic properties

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Introduction

The persistence of blood flow in abdominal aortic aneurysms (AAA), called endoleaks, is the main limitation of endovascular aneurysm repair with stent-grafts [1]. To avoid this phenomenon, several methods have been proposed, including sac embolization. However, the true efficacy of current embolic agents has not yet come up to expectations. This can be due to incomplete embolization or to recanalization of the thrombosed by endothelialized neochannels [2]. Our previous work indicates that combining embolization and endothelial ablation using an embolic agent with sclerosing properties could be a promising strategy to prevent endoleak persistence or recurrence after EVAR. This approach, based on sclerotherapy approach, consists in causing irreversible injury to the endothelial lining in the aneurysm to prevent recanalization process and induce fibrosis. In a clinical setting, this could be accomplished by injection of a sclerosing and embolic agent. The aim of this study was to develop and characterize a new injectable radio-opaque hydrogel combining embolization and sclerosing properties. Its potential for embolization of aneurysms was also evaluated *in vivo*.

Materials & Methods

2% w/v radio-opaque chitosan hydrogels containing 12% w/v β-glycerophosphate, 20% v/v contrast agent and different sodium tetradecyl sulfate (STS) concentrations (0.1, 1, 2 and 3% w/v) were prepared. Rheological measurements were carried out using the Bohlin CVO rheometer to evaluate the kinetic of gelation and mechanical properties of the gels. The time evolution of storage modulus (G') and loss modulus (G") was determined within the linear viscoelastic region. The gelation time was then determined as a function of temperature, as well as a function of STS concentration. After one week of gelation at 37°C, G' and G" of chitosan/STS hydrogels were evaluated. The morphology of lyophilized chitosan/STS hydrogels was observed by scanning electron microscopy (SEM). Cells viability was performed by Alamar Blue Essay, according to ISO 10993-13. Indirect cytotoxity essay of chitosan/STS hydrogels (0, 0.1 and 0.3% of STS) were carried out using L929 cells ($2x10^4$ cells per well). Cells were exposed for 24h to culture media incubated for different time points (24, 48, 72 and 96h). Alamar Blue (10%) was then used and cells viability was measured using fluorescence spectroscopy (λex at 540nm and λem at 590nm). Preliminary *in vivo* testing was carried out in a canine bilateral iliac aneurysms model (3 dogs) reproducing persistent endoleaks after EVAR as previously published [3, 4]. Embolizing agents were slowly injected in the aneurysms by catheter. In each animal, one aneurysm was injected with chitosan/STS3% hydrogel while the controlateral side was injected with chitosan hydrogel. The ability of the hydrogel to prevent endoleaks was determined by angiography and ultrasound imaging follow-up, as well as histology at 3 months.

Results & Discussion

Injectable radio-opaque chitosan hydrogels with and without sclerosing properties were created. All hydrogels had physiological pH. Rheological data showed that both moduli (G' and G") depend on STS concentration. The value of the initial storage modulus (G'_0) greatly varied depending on STS composition. STS concentration equal to or over 1% led to significantly higher G_0'. In contrast, G'_0 of chitosan/STS0.1% was lower than chitosan without STS. The same tendency was obtained after one week of gelation at 37°C. SEM observations showed a typical porous structure with interconnected pores for chitosan hydrogels. Addition of STS led to smaller porosity, smaller pore diameter and decreased interconnectivity.

The *in vitro* results showed that cytotoxicity was observed only with chitosan hydrogels extracts obtained at 24h. This was expected since STS is a sclerosing agent which can be released from the chitosan hydrogel. After 24h incubation, hydrogels did not release cytotoxic compounds anymore suggesting that the hydrogel rapidly becomes biocompatible.

At 3 months, no endoleak was detected in any of the 3 aneurysms treated with chitosan/STS hydrogels. In contrast, type I endoleaks were detected in 2 of the 3 aneurysms treated with chitosan hydrogels. However, no aneurysm shrinkage was observed on either side due to slow degradation of the gel. Histology showed inflammation on both sides and limited invasion of fibrous tissue inside the gel matrix. Tissue necrosis was also observed in chitosan/STS treated aneurysms.

Conclusions

An injectable radio-opaque hydrogel with sclerosing properties was developed. Rheological results suggest that chitosan/STS hydrogels are promising biomaterials for embolization of AAA. The *in vitro* and *in vivo* data suggest potential benefit of combining embolization with endothelial denudation for the treatment or the prevention of endoleaks after EVAR. However STS3% hydrogels led to extravasation necrosis. Lower STS concentration could be more appropriate.

References

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