Optimization and characterization of a new injectable radiopaque chitosan-based embolizing hydrogel for endovascular therapies

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Statement of Purpose: The development of minimally invasive procedures and tissue engineering strategies has led to a growing need for injectable materials. This is particularly true in the case of endovascular aneurysm repair (EVAR). This minimally invasive treatment of abdominal aortic aneurysms (AAA), a localized dilatation of the abdominal aorta, consists in deploying a stent-graft to exclude the aneurysm from blood flow and prevent it from rupturing. The clinical success of this procedure is however limited by frequent persistence or recurrence of blood flow inside the aneurysm, called endoleaks, which can lead to aneurysmal growth and increased risks of rupture. To treat or prevent endoleaks, sac embolization is increasingly performed by injection of an embolic agent to occlude the blood flow which persists to enter the aneurysm. However, current embolizing agents are far from ideal and clinicians seek for new injectable agents.

We recently demonstrated that chitosan-BGP thermogels could be used to create a radioopaque injectable embolizing agent (1) but these hydrogels exhibited slow gelation and needed further optimization and characterization in regards to gelation kinetic, mechanical properties and radiopacity. Here we report the characterization and optimization of chitosan-BGP hydrogels made radiopaque with iodixanol, an iodinated X-ray contrast medium, in regards to gelation rate, mechanical properties, occlusive and mucoadhesive properties, radiopacity and biocompatibility.

Materials and methods: Chitosan with high degree of desacetylation (DDA= 94%) was purified and mixed with BGP (Sigma) and Iopamidol (iodixanol, Bracco Diagnostics Inc.) at several ratios (1). Their effect on the gelation kinetic was studied by rheology on a Physica MCR301 (Anton Paar). Evolution of both storage (G') and loss (G") moduli as a function of time at fixed temperature (37°C) was followed to determine the gelation time (sol-gel transition) and the gelation rate, defined as the linear slope of G' after gelation time.

Morphology of the gels before and after rinsing (Scanning electron microscopy, SEM), swelling, radiopacity, indirect cytotoxicity and muco-adhesion were also studied. Finally their ability to occlude blood flow was studied on an in vitro bench test evaluating the maximal pressure of liquid sustained by the gel, as a function of time after gelation and BGP and contrast agent concentrations.

Results: All solutions tested were shown able to create hydrogels at 37°C. Addition of contrast agent was shown to slow down gelation, but increasing BGP was able to counteract this effect. Radiopacity naturally increased with Iopamidol concentration and a minimum concentration of 20% v/v was identified for good visibility via x-ray. Iodixanol molecules were shown to be rapidly released in the medium. This characteristic is suitable for our application since loss of radiopacity is preferable for good imaging follow-up. Evolution of both storage (G') and loss (G") moduli showed good gelation rate and rapid increase of the mechanical properties with time. However, it is difficult to conclude whether these properties are sufficient to occlude blood flow. Therefore the maximal pressure sustained by the gel in the in vitro bench test was determined, as a function of the nature of the embolization agent and embolization time.

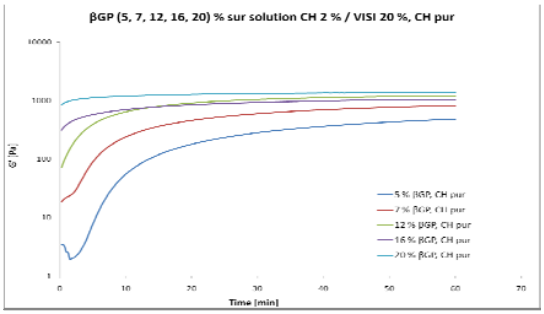

Figure 1: Effet of BGP on gelation kinetic of CH-Iodixanol hydrogels at 37 C

7 days after gelation, all gels supported up to the maximum pressure created by the bench system (>220 mmHg). At shorter timepoints, the pressure sustained by the gels increases with the BGP concentration. This can be explained by the strong effect of BGP on the gelation kinetic (Fig 1). Thus, solutions containing βGP of 12% or higher exhibit immediate gelation and a high gelation rate which allow to reach G' of 100Pa or more within one minute. SEM of the radiopaque chitosan hydrogels showed that their pores tend to be smaller when increasing BGP or contrast agent concentration. However the morphology of the gel after 24h rinsing in solution led back to a nice and typical porous structure with interconnected pores. Indirect cytotoxicity tests on released product showed a decrease of cell viability related to products released during the first 24h (probably BGP and Iodixanol). However, this must be put in perspective compared to the high toxicity of current used embolic agents (DMSO used with Onyx, cyanoacrylates etc.). Moreover extracts obtained after 48h and 72h showed no toxicity, suggesting that the hydrogels rapidly becomes biocompatible.

Conclusions: Although further evaluation is required high DDA chitosan radiopaque hydrogels with a concentration of 20% or 30% v/v iodixanol appear as a promising material for embolisation.

References: (1) Coutu et al. A new radiopaque thermogel for treatment of endoleaks after endovascular repair: Influence of contrast agent on chitosan thermogel properties. JBMR-B 2012 (online)

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