Injectable Poly(vinyl alcohol) Hydrogels for Nucleus Replacement

Berlin, J; *Braithwaite, G
*Cambridge Polymer Group, Boston, MA
Senior author gavin.braithwaite@campoly.com

Introduction: Lower back pain affects over 65 million people in the US [1] with an estimated 12 million of these cases arising from degenerative disc disease [2] (DDD). DDD is largely considered a natural progression of the aging process of the intervertebral disc (IVD) through life, and virtually all people will have DDD to some extent, although usually asymptotically. Internal disc disruption (IDD) results from damage to the disc, and is the most common detectable cause of chronic lower back pain, with a prevalence of at least 39% in lower back pain sufferers [3]. IDD usually accelerates DDD and is characterized by degradation of the nucleus and radial tears in the annulus [3] and compromised biomechanics. A significant number of patients undergo surgical intervention, which is usually invasive and often only partially successful over the long term. An ideal replacement for the damaged nucleus would be an incompressible, viscoelastic, space-filling and highly hydrated hydrogel similar to the healthy nucleus. We present here a way to use partially hydrolysed PVA hydrogels as an in situ nucleus replacement by controlling solvent quality [4]. This process affords a minimally invasive treatment for early forms of degenerative disc disease that can be performed in an outpatient setting. Results presented here validate the material and method of manufacture, prove its suitability in the loading environment likely to be encountered, and also outline a general surgical approach suitable for a minimally invasive outpatient treatment.

Materials and Methods: PVA hydrogels were made by dissolving PVA in deionized water (98°C) for approximately 45 minutes. Hot poly(ethylene glycol) (PEG) was then added to the solution as a gellant and mixed for 15 minutes. On cooling, this mixture gels at physiological temperatures to an elastic solid within minutes. The gelation mechanism is a physical hydrogen-bond crystallization process that therefore produces no toxic byproducts or unreacted materials and exhibits no reaction exotherm. The final PVA concentration for these gels is approximately 10% w/w with the remainder water.

Although all of the materials used in this hydrogel are generally considered safe, they were validated for safety using in vitro tests. In vitro cytotoxicity and endotoxicity tests were performed on gamma sterilized samples to verify biocompatibility. Cytotoxicity studies were performed and graded using the ISO agarose overlay method [5]. Endotoxicity studies were performed using the limulus amebocyte lysate (LAL) method. Results were compared to FDA requirements for a medical device contacting cerebral spinal fluid (<0.06 EU/ml) and the ISO requirements for cytotoxicity.

An ex vivo animal model was developed to assess gelation of the PVA hydrogel solution and to validate the proposed surgical strategy. A porcine lumbar spine was cut into sections composed of three full intervertebral discs using a bone saw. The space is likely to be denucleated first to remove existing tissues. A commercial tool (Hydrocision SpineJet®) was therefore used to resect and aspirate the native nucleus. The spinal segment was then equilibrated at 40°C for 3-4 hours in water. A 16G needle was inserted through the annulus into the nuclear space to provide pressure relief during injection. In surgical practice, an access cannula would fulfill this role. The hydrogel solution was injected into the nuclear space through the same pathway used for denucleation using a 16G needle until the solution was seen exiting the pressure-relief needle. Following hydrogel injection into each disc, the spinal segment was maintained in water for 24 hours at 40°C, mimicking post-surgical conditions. The segment was then removed from the water and each disc was dissected by cutting through the midline of the annulus.

A novel dynamic fatigue model was developed based on a draft ASTM guidance document (WK4863) using a silicone rubber annulus. In this case, the rubber was manufactured with a 5 mm hole to mimic an annular defect. In contrast to the ASTM document, porous end-plates were used to mimic the partial permeability of the vertebral end-plates. This approach allows the hydrogel to hydrate/dehydrate as it might in the in vivo setting. The entire assembly was mounted on an MTS MiniBionix II load-frame in a water bath at 40°C. Following a 15-minute equilibration period, chosen as a reasonable “rest” time in an outpatient setting, the composite hydrogel-rubber “disc” was subjected to 500,000 loading cycles at 2.75 ± 0.25 kN and 1 Hz. The control was an empty annulus representing a denucleated disc. Post-testing, the hydrogel was removed from the fixture, sectioned, and dried for solids content analysis. Testing on this apparatus was performed with a 5 mm circular hole representing a compromised annulus.

Results: Preliminary results demonstrate the feasibility of a new process for producing PVA hydrogels suitable for use in nucleus pulposus replacement without the use of chemical cross-linkers, irradiation or thermal cycling. The cytotoxicity and endotoxicity tests on the gel components all met FDA requirements for a medical device contacting cerebrospinal fluid. All cytotoxicity tests scored a grade 2 or better, meeting ISO requirements for a medical device. Endotoxicity tests revealed toxin levels below 0.05 EU/ml for all components.

Surgical injection of the hydrogel solution into porcine intervertebral discs was readily performed through a 16G needle. The resulting hydrogel was an intact artificial nucleus in the annular space 24 hours post injection (Figure 1). In vitro extrusion studies indicate that the hydrogel nucleus will not expel from the annular space at forces up to 3 kN through a 5 mm circular injection site. Preliminary fatigue analysis indicates that the renucleated sample crept less than the denucleated sample. In addition, the complex modulus of the composite disc was higher, implying that the renucleated disc is stiffer than the denucleated one. Both of these results are as one might expect for the natural case and support the idea that replacing the nucleus will help support the IVD by “inflating” the annulus. Post-fatigue inspection of the implant indicated a final solids content of 10%, with no visible debris, and no mechanical change to the hydrogel implant over the 500,000 cycles.

Discussion: Our early data on the injectable PVA hydrogel-based nucleus implant device suggests that it is biocompatible and readily manufactured in a laboratory setting. It also gels in situ at body temperature, and is mechanically stable in short-term mechanical tests. The ex vivo surgical procedure using the Hydrocision SpineJet® is comparable to procedures currently under consideration in artificial nucleus implantation, and works very well with the described hydrogel.

Further preliminary work examines the introduction of a radiopacifier into the gel to intraoperatively visualize disc filling, vital for fluoroscopic surgical use. Preliminary data suggests that it is possible to introduce the radiopacifier into a similar gel formulation without a significant change in the final material properties. A sterile mixing device similar to a hand-held static extruder is also underway. With the addition of these two features, it will be possible to inject the hydrogel into an empty disc space in an outpatient setting with minimal surgical difficulty. This technology could reduce the invasiveness, cost and complexity of surgical treatment for degenerative disc disease.

Figure 1: Results of gelation validation for: (a) ungelled; and (b) fully gelled formulation in the ex vivo porcine IVD

References:

Acknowledgements: Our thanks to Dr. Lou Jenis for his assistance and advice throughout this project.