

Investigation of growth factor-immobilized bioactive porous beads for the treatment of urinary incontinence

In Gul Kim¹, Se Heang Oh¹, Ji Young Lee², Ji Youl Lee², Jin Ho Lee¹

¹Dept. of Advanced Materials, Hannam Univ., Daejeon, South Korea,

²Dept. of Urology, Catholic Univ., Seoul St. Mary's Hospital, Seoul, South Korea

Statement of Purpose: Urinary incontinence, which is defined as the involuntary loss of urine, causes serious medical and social problems, having a deep influence on a patient's psychological state [1]. Stress urinary incontinence, one type of the urinary incontinence, may be caused by urethral hypermobility and/or intrinsic sphincter deficiency [2]. The main idea for the treatment of stress urinary incontinence has been referred to increment of urethral resistance to intra-abdominal pressure by coaptation or narrowing of the urethral lumen. Injectable bulking agents, such as polytetrafluoroethylene particle, silicone particle, carbon particle, glutaraldehyde cross-linked collagen, and autologous fat, have been used in the treatment of stress urinary incontinence. However, injection volume decrement with time caused by particle migration and resorption in the body has been main problems for them. In this study, we prepared growth factor-immobilized porous polycaprolactone (PCL)/Pluronic F127 beads as an injectable and bioactive bulking agent which can provide bulking effect and stimulate the defect tissues around urethra for the effective treatment of urinary incontinence.

Methods: The PCL/F127 porous beads were fabricated by an isolated particle-melting method (for nonporous beads) and the following melt-molding particulate-leaching method (for porous beads) developed by our laboratory [3]. To fabricate the porous PCL/F127 beads, the dried PCL/Pluronic F127 and salt particle mixture were placed into a brass mold (diameter, 18 mm; thickness, 2.5 mm) and thermally compressed. During this step, the Pluronic F127 can be stably entrapped within the molten PCL matrix owing to the hydrophobic interactions between PPG chains in Pluronic F127 and PCL chains. Finally, the PCL/F127 porous beads were obtained after washing in excess water to leach out the salts from the beads and vacuum drying. The Pluronic F127 chains exposed onto the PCL bead pore surfaces were used to bind heparin and the following growth factors (bFGF or VEGF) which may improve the sphincter muscle function around the urethra by the induction of smooth muscle cells. To this, the PCL/F127 porous beads were immersed in each heparin (2 mg/mL) and growth factor solution (200 ng/mL), sequentially. Their morphology, growth factor release behaviors, model cell culture (using muscle-derived stem cells, MDSCs) in the growth factor-immobilized porous bead (*in vitro*) and the animal study (using an urinary incontinence rat model) to investigate the effectiveness of the porous beads as a bioactive bulking agent (*in vivo*) were conducted.

Results: It was observed that the random-shape PCL crushed particles were changed into spherical nonporous beads with similar sizes through the isolated particle-melting method. The porous beads fabricated by the melt-molding particulate-leaching method showed highly uniform pore structures. From the growth factor release

experiment, it was observed that the growth factors immobilized onto porous PCL/F127 porous beads were continuously released up to 28 days, regardless of growth factor types. From the study of *in vitro* smooth muscle cell differentiation using muscle-derived stem cell as a model cell, it was observed that the growth factor-immobilized porous beads have positive effect for the smooth muscle cell differentiation which may promote the regeneration of damaged smooth muscle around urethra, and thus can effectively treat the urinary incontinence. In particular, the bFGF-loaded porous beads showed more effective induction of the smooth muscle cell differentiation than other groups. We also confirmed that the growth factor-immobilized porous beads have a significantly faster smooth muscle regeneration and higher cure rate for the urinary incontinence than other groups from the *in vivo* animal study (Figure 1). From the results, it was expected that the growth factor-immobilized PCL porous beads may be a good candidate as an injectable bioactive bulking agent.

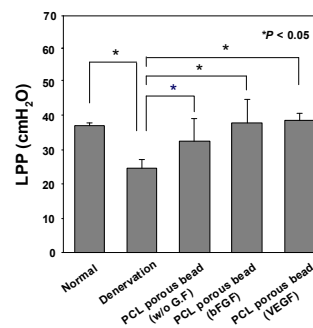


Figure 1. The leak point pressure (LPP) at 4 weeks after the injection of PCL porous beads (with and without growth factors) around the urethra of SD rat.

References:

1. Abrams P, et al., Scand J Urol Nephrol Suppl. 1988;114:5-19.
2. Blaivas J, et al., J Urol. 1997 ;157 :818-820.
3. Lim SM, et al., J Biomed Mater Res. 2009;90B: 521-530.

Acknowledgments: This research was supported by Pioneer Research Program for Converging Technology through the Korea Science and Engineering Foundation funded by the Ministry of Education, Science and Technology (M10711060001-08M1106-00110).