Hybrid Biomaterial of PLGA Microspheres and Hyaluronic Acid as a Potential Injectable Bulking Agent for Urologic and Dermatologic Applications

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Abstract

Materials currently used as an injectable bulking agent in the dermatologic and urologic fields revealed several drawbacks such as particles migration, inflammatory reaction, allergic reaction, rapid volume shrinkage, and necessity of a donor site.[1] In this study, we have developed injectable biomaterial comprising poly(DL-lactide-co-glycolide)(PLGA) and hyaluronic acid gel to overcome these problems. PLGA is a biocompatible synthetic material and hyaluronic acid[2] is a common substance found in living organisms. We examined the feasibility of injection through needle and tested biocompatibility in animal model. After transplantation, injected sites and distant organs were examined histologically to verify a new tissue formation, inflammation, and particles migrations. Injected volume was maintained approximately 80 percent for 2 months. Results demonstrated that the developed material was injectable through various gauges of needles and induced a new bulking tissue formation without serious inflammatory reaction.

Introduction

Injectable biomaterials offer many advantages over conventional surgical operations. It can be applied to treat facial wrinkles or folds, and urinary incontinence.[3,4] It is less painful, saving performing time and the cost, and easier procedure which would give better satisfaction to doctors and patients. At the present time, most widely used injectable materials are silicon, Teflon paste, animal collagen, and autologous fat.[3,5] Despite their therapeutic efficacy, their applications in medical purposes were limited by its shortfalls. Permanently remaining substances like Teflon or silicon provoked inflammatory reaction so some of the treated patients needed removal operations.[1] And

injected materials were sometimes migrated to even distant organs such as lung or liver, they blocked blood vessels.[6] Bovine collagen is not completely compatible with human. It has shown allergic reaction for 3~5% of treated people.[3] Although autologous fat seemed to be a perfect material for augmentation, it is unable to maintain its initial volume and fat source is limited.[5] Therefore we developed an injectable matrix, PLGA microspheres with hyaluronic acid gel. Both materials were tried in clinical treatment for decades and proven to be relatively safer substance than any others. It is biocompatible and biodegradable material which lasts its volume over time.

Materials and Methods

Poly(DL-lactide-co-glycolide) with a copolymer ratio of 75:25 having an average molecular weight of 100,000 was used to fabricated microspheres. Microspheres were prepared by using a conventional emulsion(o/w) solvent extraction/evaporation technique. Resulting particles were filtered into size range of 70~100㎛[7].(Fig 2) These particles were mixed with 1%(w/v) hyaluronic acid dissolved in physiological saline. 0.1%(v/v) Tween 80 was added as a surfactant.

Mixed materials were tested the feasibility of injection through syringe needle. After *in vitro* test, it was injected into the subcutaneous dorsum of mice. Each sites were injected 0.2cc.(Fig 3)

Result and Discussion

PLGA microspheres with hyaluronic acid mixture was injected through 24 gauge needle without morphological deformation of microspheres. We injected microspheres into the subcutaneous dorsum of mice to determine if the microspheres can induce a new tissue formation *in vivo*. Post implantation, we sacrificed mice and harvested implant according to the time plan. The volume(Fig 1) of the implant was maintained approximately 80% over 2 months. Histological analysis of the injected site revealed few evidence of inflammation.(Fig 4) To determine whether particles migrate, several distant organs such as lung, liver, spleen, brain, and kidney were examined by serial cut. However, there was no sign of migration in these organs.

Injected microspheres in vivo successfully formed a hybrid tissue structure which

combined with microspheres and migrated host cells from adjacent tissue. Newly formed tissue may change anatomy of the wrinkles, labial fold, ureterovesical junction, or bladder neck to improve symptoms. However, developed matrix could not persist its original volume because PLGA and hyaluronic acid are biodegradable polymers. We presume that some portion of newly generated tissue may have become neighbouring tissue, but it is not yet proven.

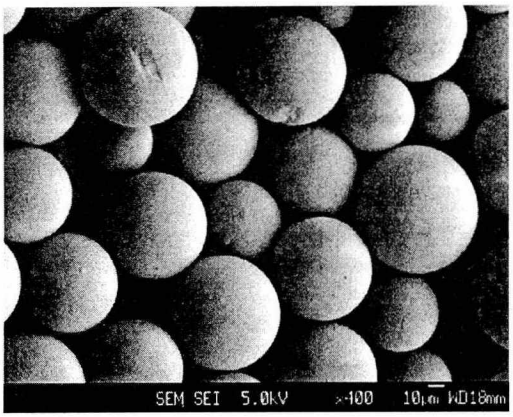

Fig 1. PLGA microspheres.

Fig 2. Injection into the mouse.

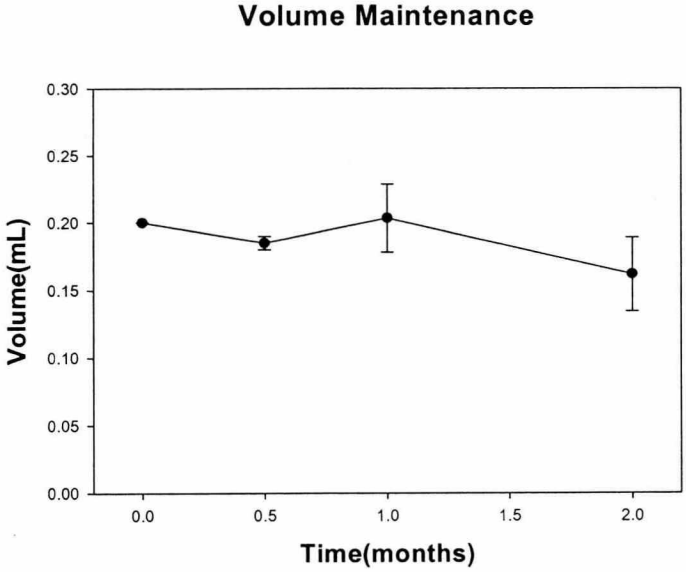

Fig 3. Injectec volume changes.

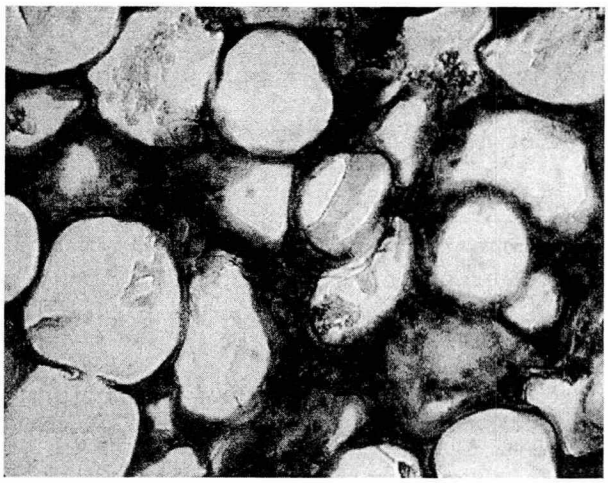

Fig 4. Histologic analysis by H&E staining (×400).

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