Studies on gelatin-based hydrogels with co-immobilized finibax and heparin for regenerative medicine

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https://doi.org/10.15017/2534414

出版情報：Kyushu University, 2019, 博士（工学）, 課程博士
バージョン：
権利関係：

（様式２）

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論文名：Studies on gelatin-based hydrogels with co-immobilized finibax and heparin for regenerative medicine
（再生医療のためのフィニバックス/ヘパリン共固定ゼラチンベースヒドロゲルに関する研究）

区　　分：甲

論　文　内　容　の　要　旨

Numerous different types of injury damage to the skin, while pressure ulcers (PUs) are recognized in millions of individuals every year. Significant healthcare problems of PUs associated with morbidity, mortality, and quality of life that affect up to 23% of bed-ridden patients in long-term care. Gels, creams, ointments, and surgery have been used to replace PUs. However, these healing methods sometimes cannot cure enough (50% of PUs heal for half-year) as less support in skin functions, for this reason, not only PUs healing problem still remained, but also it is important to enhance of wound care.

For PUs healing, researchers have focused discovering a new treatment and improving the effectiveness of healing methods, such as the administration of growth factors (GFs) for wound repair. Hydrogels have received significant attention as appealing scaffold materials for wound treatments. Generally, protein-based hydrogels consist of collagen and gelatin are a great concern through their generally exhibit a highly porous structure, softness, good biodegradability and enhanced biocompatibility, which could greatly suppress the foreign body reaction for in vivo application.

Importantly, hydrogels have received considerable attention in the past 50 years, due to their exceptional promise in wide range of applications. With the establishment of the first synthetic hydrogels by Wichterle and Lim in 1954, a variety of synthetic and naturally derived materials used to form hydrogels for tissue engineering scaffolds. Generally, hydrogels are composed of hydrophilic polymer chains, which are either synthetic or natural in origin. Protein-based hydrogels containing collagen and gelatin are great interest because their generally exhibit a highly porous structure, softness, relatively good hydrophilicity, biodegradability and also enhanced biocompatibility, which could greatly suppress the foreign body reaction for in vivo application.

As mentioned above, biomaterials have been utilized as hydrogel scaffold materials for tissue engineering. In this study, the material designs of some types of tissue-engineered products (protein, sGAG, GFs and ABA) are introduced. These designs are based on the concept of wound healing mechanism. On the other hand, we developed the antibacterial- agent heparin immobilized gelatin based gel and a nonsurgical procedure that used to create PUs using magnets through a dorsal skin on ICR mice was adapted and the efficacy of wound closure was assessed with the gelatin- based heparin hydrogel and gelatin- based ABA-heparin hydrogel with bFGF and FBS.

The dissertation is arranged into several chapters as follows:

Chapter 1 introduces the motivation and background for the study. It also stated the core of our study and poses major problems that the research intends to solve. Figure 1.3 demonstrates the hydrogel

composition and Figure 1.4 indicates a graphical abstract of this thesis. The preparation and evaluation of the hydrogels for both in vivo and in vitro studies was designed in chapter 3 to chapter 5.

Chapter 2 demonstrates the skin structure and function, skin problems such as pressure ulcers, and the current situation of wound healing. It also clear with treating managements, tissue-like structures used in tissue engineering, the main concept of biomaterials and their role in PUs healing were also mentioned.

Chapter 3 provides prior evaluations of finibax-immobilized gelatin hydrogel such as the ABA selection, their effective concentration, the immobilization of ABA and the crosslinking potential with EDC/NHS as well as antibacterial activity and release study after the immobilization. Developed Finibax-Gela gel was tested in *E.coli* culture, cytotoxicity, and subcutaneous implantation in rats by H&E staining. Experimental results were compared with gelatin gel and finibax-mixed gelatin gel in finibax-immobilized gelatin gel.

Chapter 4 gathers finibax and heparin co-immobilized gelatin hydrogel at several evaluations in the experiment, namely the amount of immobilized finibax, swelling study, mechanical strength, and rheological measurements. Cell proliferation study with mesenchymal stem cells was explained including the cytotoxicity for finibax in the hydrogels.

Chapter 5 determines a detailed heparin analysis on the gel sample with the volume ratio, precipitation time, solvent component, and solubility time. The modified Alcian blue method was validated by basic requirements such as accuracy, the limit of detection, the limit of quantification, inter-and-intraday precisions, and the relative error. Protein effect was investigated by fibrous and globular proteins. Thereafter, the heparin amount in HepGela gel and Finibax-HepGela gel was quantified by the modified AB method.

Chapter 6 develops an ICR mouse model by I/R cycles and values the PUs stage. The experimental result with different kinds of the hydrogel, namely Gelatin gel, Hep-Gela gel, Finibax-Gela gel, Finibax-HepGela gel, Hep-Gela-bFGF gel, Finibax-HepGela-bFGF gel as well Hep-Gela-FBS gel and Finibax-HepGela-FBS gel was compared. A novel treat gel for PUs healing was concentrated and benchmarked against other gelatin gels. Gel efficiency was estimated for multiple experiment conditions such as PUs treating and H&E staining results.

Finally, Chapter 7 concludes with a summary of key findings, and the main points that have been found throughout the study.