A Novel Polysaccharide-Derived Hydrogel with Controllable Viscosity for Adhesion Prevention

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Statement of Purpose: Adhesions are fibrous connections between tissues and organs that form as a response to tissue injuries during surgery. They occur frequently, and often cause chronic pain after the operation. Moreover, They lead to the decrease in patient's QOL because of complications include small bowel obstruction, infertility and nerve dysfunction. One of the modalities to prevent adhesion is that an operated organ is barriered physically. Although many materials have been used as a barrier, hydrogels are outstanding canditates because they can be used easily.

Novel sodium carboxymethylcellulose (CMC)-derived hydrogel in which phosphatidylethanolamine (PE) was introduced into the carboxyl groups of CMC was newly developed. In the present study, we investigated of the relationship between the viscosity of CMC-PE hydrogel and the effects of the hydrogel in the prevention of postoperative adhesions.

Methods: CMC-PE was synthesized by the condensation of sodium carboxymethylcellulose (CMC-Na) and dioleoyl phosphatidylethanolamine (PE). The degree of condensation was varied by changing the molecular ratio of the chemical reagents used. The PE substitution ratio per sugar unit was determined by ^{1}H NMR. CMC-PE was mixed with phosphate-buffered saline (PBS) (0.01 M phosphate buffer, pH 7.4, containing 0.15 M NaC1) at 1wt% to form a hydrogel.The viscosity of the CMC-PE hydrogel were measured by a rheometer equipped with a corn plate (gap : 0.05 mm). Viscosity at the frequency of 10 rad/s is used to evaluate the hydrogel.

For evaluating the efficacy of the CMC-PE hydrogel in the prevention of postoperative adhesion, a rat intraperitoneal adhesion model[1)] was employed. The CMC-PE hydrogel (the PE substitution ratios 0.9~1.6 mol%/sugar) were applied to the peritoneal defect before abdominal closure. The control group received no treatment. Four weeks after surgery, adhesions were scored macroscopically according to their extent in a blinded manner. All data were expressed as mean ± standard deviations (S.D.). Adhesion score data were compared across groups with Shirley-Williams multiple comparison test.

Results: CMC-PE, which PE substitution is from 0.9 to 1.6 mol%/sugar, forms hydrogel. The viscosity of the CMC-PE hydrogel showed a linear increase with the PE substitution ratios per sugar unit (Fig.1), which means that the viscosity of the CMC-PE hydrogel can be controlled by the PE substitution ratio. Because of the adequate viscosity, CMC-PE hydrogel can be applied to arbitrary area with syringe.

Fig 2 shows the results of in vivo experiments. The degree of adhesions was graded from 0 to 3 using an adhesion scoring scale as follows: grade 0 represents complete absence of adhesions, grade 1 represents thin and easily separated adhesions, grade 2 represents moderate adhesions, and grade 3 severe adhesions.

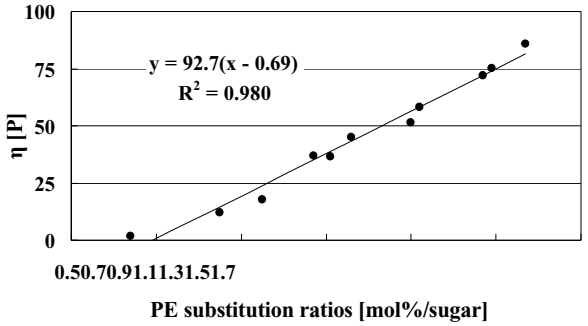

Figure 1

The CMC-PE hydrogel-treated groups showed a significant decrease of the adhesion compared to the control group, and the adhesion scores decreased with the PE substitution ratios of the CMC-PE hydrogel. Which means that, it is more effective to prevent adhesion when the viscosity of the CMC-PE gel is increased.

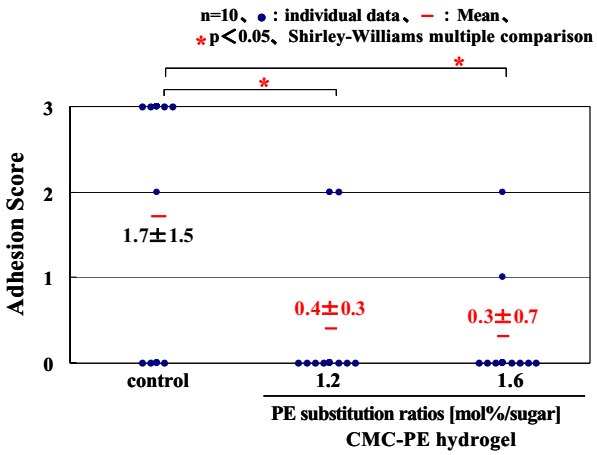

Figure 2

Conclusions: We succeeded to create a novel hydrogel of which viscosity can be controlled precisely, and to find that the effectiveness in reducing postoperative adhesions increases with the viscosity of the CMC-PE hydrogel. Further studies are needed to clarify the mechanisms of preventing adhesion.

References: 1. Buckenmaier CC 3rd. Am. Surg. 1999; 65:274-282