Postoperative tissue adhesion barrier gel based on hyaluronic acid and alginate

Seung Yeon Na[1], Se Heang Oh[1], Kyu Sang Song[2], Jin Ho Lee[1]
[1]Department of Advanced Materials, Hannam University, Daejeon, South Korea,
[2]Department of Pathology, Chungnam National University, Daejeon, South Korea

Statement of Purpose: Tissue adhesions between a traumatized tissue and surrounding organs are frequently occurring undesirable result after surgery. The tissue adhesions often induce serious complications, including patient's severe pain, functional obstruction of organs, and sometimes difficult re-operative surgery [1]. For abdominal surgery, it has reported the high frequency occurrence of postoperative intra-abdominal adhesions in 50 - 95%. To solve these problems, various synthetic and natural polymer films, nonwoven fabrics, or gels as tissue adhesion barriers have been investigated. Among them, gel-type materials have particularly been interested because they are desirable for the application on the complicated and sensitive organ tissues as well as the simple ones (injectable or coatable). Recently, hyaluronic acid (HA) gel was considered as a promising material as an effective tissue adhesion barrier, due to their biocompatibility and viscous property which can allow uniform coating around the injured site and thus act as a physical barrier. Many researchers have been reported that the HA can reduce the tissue adhesion formation in several sites, such as subcutaneous tissue, arthritic joints, tendons and peritoneal tissues [2]. However, their rapid clearance from the applied site before the healing of injured tissues is still remained as a critical limitation. In this study, we prepared HA/mildly crosslinked alginate (ALG) mixture gel to estimate its potential use as an abdominal adhesion barrier gel. We expected that the mildly crosslinked ALG with flow property can provide the residence stability of HA gel in the applied site during the healing period, and thus to keep preventing tissue adhesion. The residence stability of the HA/ALG mixture gel in the PBS was compared with that of HA and ALG gels (*in vitro*). The *in vivo* animal study using a rat model was also carried to evaluate the anti-tissue adhesion effect of the prepared HA/ALG mixture gel.

Methods: HA/ALG mixture gel (HA interpenetrated in mildly crosslinked ALG by $CaCl_2$) was prepared by a simple mixing of HA/ALG solution and HA/$CaCl_2$ solution. HA solution and mildly crosslinked ALG were also prepared as control groups. *In vitro* residence stability of the prepared samples (HA, ALG and HA/ALG mixtures) in PBS were investigated using a membrane-less dissolution model (37 ^{o}C). Animal study using a rat model was also carried out to evaluate the anti-adhesion potential, inflammatory response and granulation tissue formation of the samples. The animals were received standard surgical defects to their left peritoneal wall and cecum. Subsequently, 1 mL of the (HA, ALG and HA/ALG mixtures) were applied to the peritoneal defect side of each wound using a syringe without a needle (Fig. 1). At 7 days after surgery, the adhesion grade was blindly evaluated according to adhesion severity scale, and histological analysis at the defect site was also conducted.

Results: It was observed that the HA/ALG mixture gel shows better residence stability in PBS (37 ^{o}C) during first 7 days than that of HA and ALG gels, suggesting that the mixture gel can stably locate at the applied site and thus act as a physical barrier. From the animal study using a rat model, it was observed that the HA/ALG mixture gel was highly effective for the prevention of peritoneal tissue adhesion (Fig. 2). For the histological observations, inflammatory response and granulation tissue formation showed no significant differences among the groups, indicating the biocompatibility of the used HA and ALG.

Conclusions: From the results, we can suggest that the HA/ALG mixture gel is a good candidate material having highly effective anti-tissue adhesion and no abnormal tissue response during the healing for clinical applications as a tissue adhesion barrier gel.

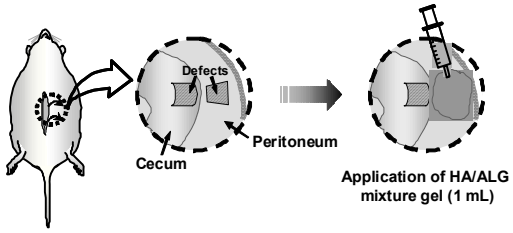

Figure 1. Schematic diagram showing the application of HA/ALG mixture gel onto the peritoneal defect of rat.

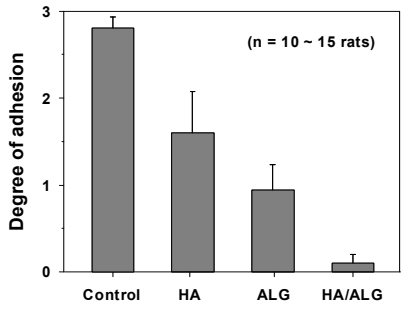

Figure 2. Comparison of peritoneal tissue adhesion of control (blank), HA, ALG, and HA/ALG mixture gel at 7 days postsurgery.

References:
1. Menzies D et al., Ann R Coll Surg Engl. 1990;72:60-63.
2. Johns DB et al., Fertil Steril. 1997;68:37-42.

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