Chitosan-Containing Bioadhesive Hydrogels as Hemostatics

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Statement of Purpose: Local hemostasis is sometimes difficult especially in patients taking anticoagulant. When the patient taking anticoagulant underwent tooth extraction, dental surgery operation, or gastrointestinal endoscopic surgery, they used to be directed to cease the intake of anticoagulant drugs for several days prior to the treatment. However, serious side effects, such as formation of thrombosis were sometimes observed. They are, thus, now instructed to continue to take the anticoagulant drugs. For such difficult-to-control bleeding, safe and efficient hemostatic device is desired.

We focused on a hydrogen bonding gel consisting of poly(acrylic acid) (PAA) and poly(vinylpyrrolidone) (PVP), which are both highly safe synthetic polymers approved and have been used as pharmaceutical excipients. When PAA and PVP are directly mixed in water, rigid gel is precipitated, which is not swelled, nor dissolved in water. Recently, we succeeded in preparation of a water-swellable PAA/PVP complex sponge under certain particular conditions. It formed a soft hydrogel on wet tissue, and strongly stick to it. It was then applied to control the bleeding after tooth extraction in patients taking the anticoagulant medicines. Soon after putting on the bleeding site, the PAA/PVP sponge swelled to a hydrogel, tightly adhered to a bleeding site, and arrested the hemorrhage effectively, even in the anticoagulated patient. However, it was sometimes difficult to achieve the satisfactory hemostasis in the patients taking high dose of warfarin.

On the other hand, it is known that chitosan (CS) has a blood-coagulating effect, and has been utilized in some hemostatic agents. Here, PAA/PVP complex sponge containing CS was prepared, and application of the CS containing hemostatic device to tooth extraction of patients taking anticoagulant was attempted.

Methods: Preparation of PAA/PVP/CS complex sponge: PAA solution was dried up to a clear film. PVP aqueous solution containing hyaluronic acid and CS was then poured upon the PAA film. It was then freeze dried, and spongy sheet was obtained.

Hemostatic effect on mice: Mice were injected with 50 IU of Fragmin, a low molecular weight heparin. They were anesthetized by pentobarbital, and the skin over the femur was incised to expose the femoral vein. Soon after cutting the vein, PAA/PVP/CS sponge was put on the hemorrhage bleeding site, and hemostatic behavior was observed.

Clinical study: Clinical study was carried out on the patients taking the anticoagulant medicine after tooth extraction. PAA/PVP/CS spongy sheet was cut into a stick, and placed on the bleeding socket, soon after the extraction, and hemostatic effect and recovery condition was observed.

Results: Direct mixing of aqueous PAA- and PVP-solutions results in formation of a water-insoluble, and –inswellable rigid precipitate. On the other hand, pouring PVP solution onto a dried PAA film afforded a highly swelled sticky hydrogel. Freeze-drying of the hydrogel gave a white spongy sheet. Addition of hyaluronic acid improved the physical properties of the sheet. In order to prepare a CS-containing PAA/PVP gel, CS powder was suspended in PVP solution, and poured onto a PAA film. PAA was similarly swelled to a sticky hydrogel, and freeze-drying of the hydrogel afforded a soft spongy sheet.

Hemostatic effect of the PAA/PVP complex spongy sheet with or without CS was examined on mice treated with 50 IU of Fragmin. The femoral vein was exposed and cut. The water-swellable PAA/PVP or PAA/PVP/CS spongy sheet was placed on the bleeding site. When the thin PAA/PVP sheet without CS was put on the heavily bleeding site, spongy sheet sometimes got a hole being dissolved by the blood, and the blood leaked out in minutes Thick, or piled sheet was required for complete hemostasis. On the other hand, CS-containing PAA/PVP spongy sheet provided higher effective hemostasis, and thin PAA/PVP/CS spongy sheet could immediately stop the bleeding.

Clinical study of the PAA/PVP complex containing CS powder to control the bleeding after tooth extraction was performed on the patient taking anticoagulant medicine such as warfarin. After tooth extraction, the PAA/PVP/CS spongy stick was placed into the bleeding socket. The sponge absorbed the blood, and swelled to a hydrogel. It adhered to a bleeding site, and arrested the hemorrhage effectively, even in the anticoagulated patients.

Conclusions: Water-swellable PAA/PVP complex sponge containing CS powder could be obtained under certain particular conditions. It showed high hemostatic efficiency in mice treated with a large amount of heparin. Excellent efficacy of the sponge as a hemostatic device was also confirmed in the clinical studies, and no adverse side effect was as yet observed. Further clinical study is now ongoing.

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