

## Novel Biodegradable Devices Forming Bioadhesive Hydrogels for Hemostatics and Adhesion Barriers (2):

### Preparation of Hemostatic Sponges and Clinical Application in Dental Surgery

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**Statement of Purpose:** Local hemostasis after tooth extraction or dental surgery operation is sometimes difficult especially in the patients taking anticoagulant. It used to be recommended to stop taking the drug at least 3 days before the surgical procedure. However, stopping the drug exposes the patient to serious vascular problems such as thromboembolism. Recently, it is said that the anticoagulant therapy should not be discontinued before tooth extraction.

Usually, after tooth extraction, gauze pack is placed on the extraction site to control bleeding. The patient is advised to firmly bite on the gauze for at least 30 min. For hard-to-control bleeding, topical hemostatic device is applied. Absorbable sponges consisting of oxidized regenerated cellulose or bovine proteins are widely used. However, they are not adhesive to the bleeding site, and sometimes it should be sutured. Risks of infection or inflammation by the foreign proteins are not completely eliminated.

A soft hydrogel which adheres to a bleeding site is expected to effectively control the bleeding. Poly(acrylic acid) (PAA) is known to form a bioadhesive hydrogel. PAA forms water-insoluble complex with poly(vinylpyrrolidone) (PVP) in water. Recently, we found that under certain particular conditions, water-swallowable composite film of PAA and PVP could be obtained. It absorbs water to form a hydrogel, which firmly adheres to a tissue. In this study, fluffy sponge type of a water-swallowable PAA/PVP composite was prepared, and application to a hemostatic device after tooth extraction or oral surgery was examined.

**Methods:** Preparation of PAA/PVP spongy sheet: PAA solution was dried up to a clear film. PVP aqueous solution was then poured upon the PAA film. It was then freeze dried, and white spongy sheet was obtained. Hyaluronic acid (HA)-containing sponge was similarly prepared by adding HA to the PVP solution, previously.

**Hemostatic effect on mice:** Mice were anesthetized by pentobarbital, and the skin over the femur was incised to expose the femoral vein. Soon after cutting the vein, PAA/PVP/HA sponge was put on the hemorrhage site, and hemostatic behavior was observed. The degradation behavior of the sponge was examined with fluorescence-labeled PAA/PVP/HA sponge.

**Clinical study:** Clinical study was carried out on the patients who underwent tooth extraction. PAA/PVP sponge was placed on the bleeding socket, soon after the extraction, and hemostatic effect and recovery condition was observed.

**Results:** All the materials contained in the sponge are highly safe, and approved as pharmaceutical excipients. Mixing of aqueous PAA and PVP solutions results in formation of water-insoluble, and -inswallowable precipitate. On the other hand, when the complex was prepared by

pouring PVP solution onto a dried PAA film, lyophilization afforded a water-swallowable white spongy sheet (Fig. 1). It immediately formed a soft hydrogel on a wet tissue, and stuck to it (Fig. 2). The resulting PAA/PVP hydrogel was slowly dissociated at pH 7.4.



Fig. 1 Water swellable PAA/PVP spongy sheet

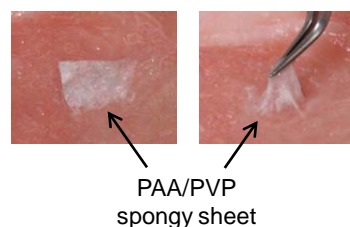


Fig. 2 Adhesion of the PAA/PVP gel to the tissue

Clinical study of the PAA/PVP complex to control the bleeding after tooth extraction was performed on the patient taking Bayaspirin, an anticoagulant preventing blood clot formation. After tooth extraction, the PAA/PVP complex sponge was placed into the 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 patient. (Fig. 3).



Fig. 3 Hemostatic effect of PAA/PVP sponge on dental surgery

**Conclusions:** Water-swallowable PAA/PVP sponge could be obtained under a certain condition. It showed high hemostatic efficiency in the clinical studies, and, as yet, no adverse side effect has been observed. Further clinical study is now ongoing.

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