

REVIEW

Yasuko Tomizawa, MD

Clinical benefits and risk analysis of topical hemostats: a review

Abstract A variety of local hemostats including absorbable gelatin sponge, collagen hemostat, and oxidized cellulose are commercially available. Local hemostats are applied when cautery, ligature, or other conventional hemostatic method is impractical. Proper handling is essential to control bleeding and only the required amount should be used, even though the hemostat is expected to dissolve promptly. A dry local hemostat absorbs body fluid of several times its own weight and expands postoperatively. Therefore, when an absorbable hemostatic agent is retained on or near bony or neural spaces, the minimum amount should be left after hemostasis is achieved. Documentation is important with regard to the hemostat used, including the name of the agent, site, and amount. This information is used as a reference in the interpretation of postoperative diagnostic images, since retained hemostat may sometimes mimic an abscess or recurrent tumor. The antigenicity of collagen is known to be low because of homology. When the safety of collagen was evaluated, the incidence of positive reactions was reported as 3.0%, and collagen may cause allergic reactions. Minimum inflammation without strong foreign body reactions or blockade of healing is desirable after the use of local hemostats. Strong foreign body reactions, chronic inflammation, and infections can cause granuloma formation after local hemostat use. By using local hemostats, it is possible to improve the condition of the patient, reduce complications, and lower direct and indirect costs.

Key words Local hemostat · Collagen · Biomaterial · Granuloma

Introduction

Local hemostat can be used to arrest suture hole bleeding and bleeding from the cross-sectional surface of parenchymatous organs such as liver and spleen. The direct benefits of local hemostats include improving blood conservation by reducing blood loss, avoiding the adverse effects of systemic hemostatic drugs, saving transfusion blood, and shortening the time of hemostasis and time spent in the operating room (OR). As indirect benefits, the use of local hemostat may cut down the intensive care unit (ICU) stay and the hospital stay, and consequently is economically valuable.

Local hemostats are applied when cautery, ligature, or other conventional hemostatic method is impractical. In this article, the benefits and risks of local hemostat use are reviewed.

Progress of hemostats

From antiquity, woven cotton gauze was used to stop bleeding, but its hemostatic action was not satisfactory, and various kinds of tissues were applied for hemostasis. In 1915, Grey¹ used fibrin from sheep blood and found it much better than using cotton. Harvey² made the first dry fibrin dressing in 1916. Later, oxidized cellulose was developed by Frantz.³ Physiologically absorbable gelatin foam or sponge was thought to be beneficial and was introduced in 1945.⁴ However, only limited hemostatic action was obtained by these local hemostatic agents.

A wide variety of local hemostats have become commercially available. Currently, there are many choices of hemostatic products such as gelatin sponge/powder; collagen sponge/powder/fiber/sheet; oxidized cellulose; thrombin; collagen combined with hemostatic agents such as aprotinin, thrombin, and fibrin sealant; gelatin with thrombin; and fibrin glues. These products are categorized according to site and degree of bleeding, which is helpful for surgeons.

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Y. Tomizawa (✉)
Department of Cardiovascular Surgery, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
Tel. +81-3-3353-8111 (ext. 23111); Fax +81-3-3356-0441
e-mail: 4CRNRY@hij.twmu.ac.jp

Proper handling of local hemostats is essential to control bleeding, and for that, the form or configuration of local hemostat is an important factor. Hemostats in the form of gauze, sheet, sponge, and fleece are the most popular. The gauze and flocculate forms are satisfactory in terms of operability, but the fleece and powered forms are not satisfactory in terms of handling characteristics because they have high electrostatic charge and stick to instruments and gloves. The fiber form and cotton-type collagen improve both the handling characteristics and the effect of arresting hemorrhage. The best results have been obtained when the diameter of the fiber is 20–50 μm . When the thickness of the fiber becomes too small, the effect of arresting bleeding is lessened.⁵

Characteristics of collagen

Collagen is a tissue-derived biomaterial, and collagen-based materials currently available for medical use include sutures, hemostats, substitute for pericardium, wound dressing, burn dressing, vascular graft coating, soft-tissue augmentation, and material for treatment of urinary incontinence. As a biomaterial, collagen is known to possess the characteristics of high tensile strength, high affinity with water, low antigenicity, absorbability in the body, good cell compatibility (adhesion, growth, and migration), enhancement of tissue regeneration, an effect on cell differentiation, activation of platelets, properties controllable by physical and chemical modifications, and availability of variously shaped fabrications.⁶

Collagen is one of the best materials for use as a scaffold in tissue engineering, and with modification, it can be used in a variety of fields.⁶ Collagen is useful as a scaffold upon which cell proliferation and migration occurs. Angiogenesis was accelerated using cotton-type collagen as a scaffold in a wound healing model.⁷ However, commercially available collagen hemostats have different cell affinity and biocompatibility.⁸

Antigenicity and immunogenicity of collagen

The collagen molecule consists of three polypeptide chains. Tropocollagen is the molecular subunit of collagen and its nonhelical portion is composed of telopeptides. The antigenicity of collagen is known to be low because of homology. The structural complexity of collagen molecules is the source of a highly diverse antigenic structure.⁹ Telopeptides are known to be the sites with the highest interspecies variability. The immunogenic potential of the collagen molecule is strongly reduced by proteolytic digestion of the telopeptides. Atelocollagen is an enzymatically processed collagen that lacks the telopeptide region. It is solubilized and has reduced antigenicity.¹⁰

An enzyme-linked immunosorbent assay (ELISA) analysis of antibody titers to various collagen implants in a guinea pig model showed that Avitene (Avicon, Humacao Puerto

Rico) was more immunogenic than other hemostatic and injectable collagens.¹¹ Furthermore, sera from animals treated with Avitene had significant antibody reactivity with bovine serum albumin (BSA).

The safety and efficacy of an injectable collagen was evaluated in 5109 patients, and the incidence of a positive reaction was reported to be 3.0% and that of adverse treatment reactions 1.3%, most of which manifested with localized swelling and erythema.¹²

There are few clinical evaluations of immunogenicity after implantation of collagen (other than injectable collagen) in clinical subjects. In a prospective randomized study, 5 of 68 patients implanted with a collagen-coated vascular graft (Hemasheild, Meadox Medicals, Oakland, NJ, USA), developed antibovine collagen antibodies, demonstrating the potential of bovine collagen to stimulate an immune response (seroconversion).¹³ However, one patient in the control group, who had a noncollagen-coated vascular graft, also developed antibovine collagen antibodies. In the report, there is no comment about the use of local hemostats made of bovine collagen; however, there is a possibility that local hemostat of bovine origin was used and was the cause of the antibodies.

A systematic allergic reaction was reported in a patient who underwent laparoscopic cholecystectomy using Avitene.¹⁴ In this patient, the skin test revealed a notable allergic reaction to Avitene, while an immunoglobulin E/radioallergosorbent test (IgE-RAST) against bovine serum albumin was within the normal range.

Efficacy of hemostat

It is important to use a standardized method for evaluating the efficacy of hemostats. There are many animal models for evaluation of hemostasis. Bleeding from the liver, spleen, and artery in experimental animals has been used. Chvapil introduced a standardized animal model for evaluation for various materials.¹⁵ Collagen-based hemostats trigger platelet aggregation when directly applied to bleeding tissue, and a good hemostatic action for collagen has been reported.¹⁶

When platelet activation was evaluated in five substitutes in vitro, aggregation was observed with bioerodible polyorthoester and unwoven fleece but not with bone wax, oxidized cellulose, or gelatin sponge.¹⁷ Wagner et al.¹⁸ evaluated the coagulation mechanism of local hemostats in vitro and classified them in descending order of effectiveness as follows: microfibrillar collagen, collagen sponge, gelatin sponge, and oxidized regenerated cellulose. Topically used hemostat adheres to the bleeding site providing astringency and initiates platelet activation and aggregation. It also reinforces the fibrin clot.

Clinically, there have been many multicenter randomized controlled studies on the efficacy of hemostats; however, since surgeons can see the hemostat used and its effect on and hemostasis at the OR table, these studies have not been conducted double-blind.¹⁹ “The desire to prove the effectiveness of a specific hemostat” may possibly affect the results.

Information on the hemostats used, including the name of the hemostat, the site, and the amount, should be documented in the surgical record, because that information will be helpful in the interpretation of future diagnostic images.

Dissolution and absorption of absorbable hemostat

Local hemostats were evaluated subcutaneously and in muscle, the subdura, and bone in an animal experiment and tissue samples were histologically evaluated. Differences in biodegradability were seen depending on the amount used, the site of implantation, and environmental factors. Oxidized cellulose has been reported to dissolve promptly in various sites in an animal experiment with complete dissolution by 6 weeks.³ In another experiment, Surgicel was implanted subcutaneously in rats and residue was recognized in a few animals at 30 days with infection.²⁰ Surgicel (Johnson and Johnson, New Brunswick, NJ, USA) was still present at day 36 in a rat brain.²¹ In a rabbit ear chamber model, Surgicel dissolved promptly, but the residue was still recognized after 5 weeks.²² Dissolution does not always mean disappearance of hemostat from the implanted area. Even though the material dissolves in a short period, absorption of the residue and wound healing of the implanted site are two different processes.

Several case reports have indicated that residue of oxidized cellulose can be recognized at reoperation. Oxidized cellulose fibers were detected histologically near a coronary bypass graft anastomosis after 5 years and 9 months.²³ A yellowish ocher tumor was macroscopically observed 2 years and 7 months after valve replacement and it was granulomatous tissue from oxidized cellulose.²⁴ One year after aortic root replacement with a graft and resuspension of the aortic valve commissures, thick cheesy material was macroscopically observed at reoperation and found to be retained nonabsorbed Surgicel.²⁵ These reports explain earlier reports of persistence of Surgicel at sites of implantation. When a local hemostat is used and left after operation, many surgeons assume that it will be absorbed promptly. However, sometimes this may not happen, depending on environmental factors, and it is preferable to leave the minimum amount of redundant material.

Inflammation after local hemostat use

Healing quality is important after implantation of a medical device, and minimum inflammation without a strong foreign-body reaction or blockade of healing is desirable. Following the use of a resorbable hemostat, an inflammatory response develops around the hemostat until complete absorption is accomplished.

In a rat experimental bone defect model, histological differences in the healing process were observed between three hemostats; bone wax inhibited osteogenesis, Surgicel markedly slowed the rate of repair and caused inflamma-

tion, and Gelfoam (The Upjohn, Kalamazoo, MI, USA) achieved complete healing.²⁶ Furthermore, the effects on the pH of body fluids were evaluated in vitro, Surgicel caused a significant decrease in pH of heparinized blood, plasma, and serum.²⁷ The acidic nature of Surgicel may cause strong inflammatory reactions if remaining at the implanted sites. Removal of redundant hemostats, particularly Surgicel, from surgical sites is recommended in order to maximize healing, since the local pH surrounding a hemostat could influence the progress of inflammation and wound healing.

Observation of wound healing with local hemostats

Host cells such as macrophages and fibroblasts recognize implanted materials. Microfibrillar collagen hemostat (MCH) interfered with the initiation of dental socket healing in a rat study.²⁸ Histological evaluation of collagen hemostats has been well documented. In a rabbit subdural study, the tissue reaction to MCH is characterized by moderate to marked granulomatous inflammation with an acute inflammatory component indicating a greater degree of tissue irritation.²⁹

Clinically, Smith et al.³⁰ observed wound healing by punch biopsies after the use of bovine collagen matrix and they reported that the matrix promoted thrombosis as well as migration and attachment of stromal and epithelial cells, consequently accelerating wound healing.

Clinical application of hemostat

Antiplatelet agents and anticoagulants are commonly used in patients with cardiovascular diseases. The effectiveness of hemostats may be influenced by extracorporeal circulation using heparin, hemodilution, decreased platelet count, and impaired coagulation factors.

Collagen hemostat effectively provided hemostasis in a patient with gingival bleeding from thrombocytopenia due to leukemia.³¹ Local hemostats are effective when a large amount of blood loss is expected in dental patients on warfarin.³²

Local hemostats do not adhere strongly to wet tissue and have little impact on actively bleeding wounds. Hemostats should not be used to stop arterial bleeding. Local hemostats are potentiators of infection and should be used in the smallest quantities possible where a risk of bacterial contamination exists.

Infection and local hemostat use

Oxidized cellulose was expected to possess an antibacterial effect.³³ However, subsequent study has found that the observed resistance to infection from using oxidized cellulose was due to an acidic pH that was fatal to bacteria.³⁴ Hill³⁵

reported that a small amount of local hemostat enhanced infection. The presence of a small amount of foreign body has been observed to increase susceptibility to infection.³⁶ Surgicel lowers the pH of culture medium and decreases the number of fibroblasts, while other hemostats such as Spongel (Yamanouchi Pharmaceutical, Tokyo, Japan), Avitene, and Integran (Koken, Tokyo, Japan) do not change the pH of culture medium or decrease the number of cells.²² Hemostats should not be cytotoxic or affect host cell survival. An acidic local pH induced by local hemostats influences the surrounding tissue via the acidic tissue fluid, delaying healing. A local hemostatic agent may increase infection and should not be used in an infected wound.

Passing through the transfusion filter

Cell-savers are popularly used for the purpose of decreasing the total amount of blood transfusion. However, small particles of Avitene can pass through a filter with a pore size of 40 μm used for blood transfusion.^{37,38} Microscopically, approximately 10- μm particulates of Avitene were observed.³⁹ Using proper filters, at least 97% of total collagen can be removed.⁴⁰ However, MCH should not be used in conjunction with cell-savers to avoid the possibility of embolism.

Confusion of diagnostic imaging after local hemostat use

In neurosurgery, differentiation between residual local hemostat and a tumor or an abscess is often difficult on postoperative diagnostic images from CT scans and angio nuclear magnetic resonance (angio-NMR) scans. Misdiagnosis of a hemostat-associated mass as recurrent brain tumor resulted in reopening of the cranium in several reported cases.⁴¹⁻⁴³ Histological analysis in these cases revealed that the underlying cause of granuloma was from Surgicel.

Hemostat-associated mass lesions have been given a variety of names, e.g., textilomas, gossypibomas, gauzomas, and muslinomas.⁴⁴ Intracranial textiloma cases have been reviewed by Ribalta et al.⁴⁴ and hemostats such as microfibrillar collagen, gelatin foam, and oxidized cellulose are the most common causative agents.

Oto et al.⁴⁵ described the appearance of oxidized, regenerated cellulose on postoperative T2-weighted magnetic resonance (MR) images with a short relaxation time, resulting in low signal intensity in the early postoperative period. Spiller et al.⁴⁶ examined the effect of topical hemostats on the relaxation time (T1) of blood in contact with hemostats over time in vitro and found that they affect the interpretation of postoperative MR images. With the addition of Surgicel, blood pH was decreased and T1 was significantly shortened in all fields.

In cardiovascular surgery, misinterpretation of diagnostic images is not commonly reported, but postoperative thoracic angio-NMR images were unable to differentiate

excess Surgicel from an intramural hematoma of the ascending aorta.⁴⁷

The characteristic appearance of retained Surgicel in abdominal radiographs,⁴⁸ sonograms,⁴⁹ and CT scans⁵⁰⁻⁵² was easily identified. Abdominal abscess was suspected after laparoscopic cholecystectomy with the use of Surgicel,⁵¹ and a differential diagnosis from abscess was difficult. CT images of an abdominal abscess taken after Gelfoam had been used showed a complex air-fluid collection.⁵³ O'Connor et al.⁵² described the CT appearances of absorbable hemostats as mixed or low-attenuation masses containing a focal central collections of gas.

Nature of a local hemostat that absorbs moisture and expands

Local hemostats can absorb water/body fluid/moisture of up to several times its own weight. Oxycellulose absorbed physiological saline of 7 times its own weight, Avitene 12 times, and cotton-type collagen hemostat 32 times.³⁹ The portion of retained hemostat that has not participated in hemostasis absorbs effusion and moisture, expands, and presses the nerves in the surrounding tissue against bone or hard tissue.

In a reported case, paraplegia was diagnosed one day after thoracotomy, and was caused by spinal cord compression due to Surgicel used in surgery.⁵⁴ Brodbelt et al.⁵⁵ reported other cases with delayed paraplegia between 12h and 2 days after thoracotomy. They found that Surgicel had passed through the intervertebral foramen causing spinal cord compression. Cases of paraplegia after thoracotomy and lumbar laminectomy have been reported and occurred mostly within 24h after surgery.^{56,57} Even in an enclosed space, Gelfoam also expanded and compromised the spinal cord.^{58,59}

Histological examination of removed specimens of Surgicel revealed predominantly swollen fibers with few red cells.⁵⁵ This means that hemostat expansion is not a result of bleeding or hematoma. The Food and Drug Administration (FDA) has recommended the use the minimum amount of hemostat necessary to achieve hemostasis and the removal of as much of the agent as possible after hemostasis is achieved, when an absorbable hemostatic agent is used on or near bony or neural spaces.⁶⁰ Only the amount needed for hemostasis should be used and this should be held in place until bleeding stops; excess hemostat should be removed as far as possible after clot formation.

Migration of local hemostat can be another cause of adverse events. Dutton et al.⁶¹ reported a case of optic nerve compression by migration of Surgicel 48h after surgery.

Granuloma formation

Host fibroblasts excrete collagen to replace the residual biodegradable hemostat. However, strong foreign body

reactions, chronic inflammation, and infections may cause granuloma formation after local hemostat use, and a small piece of cotton fiber that has been retained during surgery could also be a cause of granuloma.^{44,62} Surgicel granulomas have been reported in a variety of sites including the intracranial space,⁶³ around a coronary bypass graft,²³ and after valvular surgery.²⁵ Moreover, Avitene granulomas have been recognized as an intraperitoneal tumorous mass⁶⁴ and on colonic serosa,⁶⁵ while ureteral obstruction secondary to fibrosis due to Avitene has been reported.⁶⁶

Consideration of transmissible diseases

Bovine spongiform encephalopathy (BSE) had become a topic of intense discussion since 1986, because many medical devices are based on collagen of bovine origin, mainly from the derma or tendon. There is no report of human BSE infection from collagen-based medical devices, including local hemostats. The raw material of the collagen should not come from a country with known BSE cases. The possibility that prions could be included in derma or tendon is quite low.

Economic considerations

From the economic standpoint, the use of allogenic blood transfusion together with pharmacological agents extracted from animal organs to achieve hemostasis is expensive in cardiac surgery.⁶⁷ One of the adverse effects that is related to all systemic medications is thromboembolic complications including thrombosis of a bypass graft. Aprotinin is of bovine lung origin, and a small risk of anaphylaxis still exists. It is suggested that improved hemostasis should result in indirect cost savings.⁶⁸

Many studies of hemostats in cardiac surgery address the economic issue.^{67,69} One suggestion to reduce cost in the OR is to use less expensive local hemostat instead of the expensive xenopericardium in lung reduction operations, and this achieves equally effective results.⁷⁰ Aprotinin costs approximately 100 times as much as aminocaproic acid.⁶⁷ In cardiac operations with a predicted high risk of bleeding, the cost of topical hemostatic agent treatment with associated transfusion requirements was significantly lower in the collagen hemostat group compared with the Surgicel group (\$152 versus \$202).⁷¹

Conclusions

A variety of local hemostats are available on the market. Proper handling is essential and only the amount needed should be used so as to leave the minimum amount possible. Removal of excess hemostat following achievement of hemostasis is recommended. Documentation is important

with regard to hemostat and is used as a reference in the interpretation of postoperative diagnostic images. By using local hemostat, it is possible to improve the condition of the patient, reduce complications, and lower the direct and indirect costs.

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