Comparison of Topical Hemostatic Agents:
Starch powder, Gelatin sponge or Gelatin matrix and Oxidized
regenerated Cellulose
Review of Adverse Events

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Abstract:
There are a variety of absorbable hemostats locally placed during surgery commercially available. Proper handling is essential to control bleeding and only the required amount should be used, even though the hemostat is expected to dissolve promptly. By using local hemostats, it is possible to improve the condition of the patient, reduce complications, and lower direct and indirect costs.
In this article we describe side effects of textile (or woven fabric) based hemostats. Gelatin sponge, Gelatin matrix or oxidized cellulose are currently in widespread use. Unfortunately there are product related adverse events like inflammation, foreign body reactions, Granuloma formation or blockade of healing when these devices were used. Even more compression and damage of tissue, e.g. nerves with consecutive palsy is described. One reason for this damaging effect is the late swelling of the textiles. Mimicking of structures in medical imaging, e.g. radiology or ultrasound diagnostics is as well frequently reported. Deleterious migration of the textile-based hemostats is as well described as cause of severe adverse events. A well-known complication of hemostats is the promotion of painful adhesions, especially in abdominal or gynecological procedures.
In contrast there are starch based hemostat powders with broad range of application and good hemostatic effect. To date, there are no serious product related adverse events known. Even more, there is evidence that starch powder might prevent adhesions.

**Introduction:**

Local hemostats are applied as adjuncts for bleeding control when pressure, ligature, cautery or other conventional hemostatic methods are not beneficial or not applicable. Historical normal cotton gauze and pressure was used for bleeding control. But there was always need for improvements in action and performance. In 1943 Frantz presented oxidized cellulose [1] as one of the first topical hemostats with improved performance. Another hemostat is the absorbable gelatin foam or sponge which developed was and introduced in 1945 [2]. However, the hemostatic action obtained by these local hemostatic agents was somehow limited, side effects and adverse events were reported and therefore as a logical consequence further developments were invented. One was e.g. Floseal, a gelatin matrix combined with Thrombin. Floseal has bovine components. The hemostatic effect was improved, but there are still concerns regarding adverse events.

In the late 1990th Carboxymethyl-starch products were invented for bleeding control in surgery. To date there are no major product related adverse events reported.

In the following report we review the biodegradability, absorption and adverse events of oxidized cellulose, gelatin sponge, gelatin matrix combined with Thrombin and Carboxymethyl-starch products when used for bleeding control in surgery reported in the literature.

**OXIDIZED REGENERATED CELLULOSE:**

It is said that oxidized cellulose dissolves promptly in various sites. In an animal experiment it was reported that complete dissolution is within 6 weeks [1]. In another experiment, Surgicel (Johnson and Johnson, New Brunswick, NJ, USA) was implanted subcutaneously in rats and residue was recognized in a few animals at 30 days with infection [3].

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 [4]. Even more the patient experienced graft stenosis because of the hemostat.

Migration of textile based hemostat can be another cause of adverse events. Dutton presented a case of optic nerve compression by migration of Surgicel 48h after surgery [5]. (In an unpublished case we had similar experience in our institute. After use of Surgicel for bleeding control on the heart we left the Surgicel on the bleeding area, because removal of the material caused again bleeding from the right
ventricle. Five hours later the patient needed an emergency reoperation due to occlusion of the venous bypass graft to the right coronary. This was caused from Surgicel which was moving under the venous bypass, swelling and therefore kinking the bypass-raft.) Nevertheless, manufacturers of these hemostats, e.g. Surgicel and Gelfoam, recommend the removal of the material once hemostasis is achieved. But as mentioned, removal results most times in recurrent bleeding and therefore most surgeons tend to leave it in place.

Another case demonstrating late- or non-resorption of oxidized cellulose: A yellowish ocher tumor was macroscopically observed 2 years and 7 months after valve replacement and it was granulomatous tissue from oxidized cellulose [6]. 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 non-absorbed Surgicel [7].

Textilomas may present with neuroimaging features that mimic recurrent tumor (Figure 1, Surgicel was found 6 months after first operation; Figure 2, Gelfoam was not resorbed and still present after 3 months) and giving trouble in postoperative diagnostics, e.g. mimicking tumors [8]. These hemostats (here Surgicel, Oxycel, Avitene and Gelfoam; [8]) may produce significant space-occupying mass lesions appropriately termed textilomas that are clinically and/or radiologically apparent. These reports reveal earlier reports of persistence of Surgicel at sites of implantation. When local hemostats are used and left in place of the operation side, depending on different environmental factors, the material is not resorbed in time.

![Image](image.png)

Fig. 1: Residual material of Surgicel was found in the reoperation, 6 months after primarily opration of a Glioma. This residual material was mimicking the recurrence of the tumor [8].

One of most deleterious adverse events caused by hemostats is palsy. Main reason is compression of nerves or brain-structures because the products were used in cavities, left in place during surgery and start
swelling after the operation was finished. Quite a notable amount of reports with paraplegia after thoracotomy and lumbar laminectomy have been published. Some exemplary publications: Most paraplegic complications occurred within 24 hours after the operation [9, 10]. An article published by Brodbelt [11] presented three more 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. Iwabuchi et colleagues [12] described a case of paraplegia which occurred on day one after thoracotomy. It was caused by spinal cord compression due to use of Surgicel.

Surgicel and other foreign substances that are deliberately introduced in the surgical site may induce an excessive inflammatory reaction, which produces clinically symptomatic and/or imaging apparent mass lesion as long as the material is not resorbed. When Surgicel left in place the acidic nature may be responsible for a mild to strong inflammatory reaction. However, in most cases mild reactions remain asymptomatic. Chronic inflammation, strong foreign body reactions, and infections after local use of the hemostats may result in granuloma formation. Surgicel granulomas have been reported in numerous cases including surrounding of a coronary bypass graft [4], the intra-cranial space [13] and after valve surgery [14]. However, an untamable inflammation targeting against the foreign material might produce space-occupying masses and large granulomas with clinical relevance.

It is also a well known and multiple described side effect of hemostats that they might promote adhesions. Especially when used in the abdominal cavity or in gynecological procedures for bleeding control they can cause long lasting pain. Not for use in closed spaces because. Another warning is: Do not use oxidized cellulose in bone fracture.

GELATIN BASED HEMOSTATS:

Gelatin based hemostats like e.g. GELFOAM (Pharmacia and Upjohn Company, Michigan USA) is prepared from purified porcine skin. Thus far, there are no transmissible diseases with porcine material reported. However, raw material from medical devices based from animal origin always bears this risk. But there are several reports regarding allergic reactions and anaphylactic shock reaction to the porcine material of Gelfoam [15-18]. Even in the IFU of e.g. GELFOAM PLUS (Gelfoam matrix plus human Thrombin) toxic shock syndrome has been reported in association with the use of GELFOAM Sterile Sponge in nasal surgery [19]. Continuing with IFU of GELFOAM PLUS: it is written, that it contains Thrombin made from human plasma and is not possible to remove completely all viral infectivity from derivatives of human plasma. E.g. parvovirus B19, are particularly difficult to remove or inactivate at this time. Some viruses, such as parvovirus B19 are most seriously affecting pregnant women, or immune-compromised individuals. Symptoms include fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain.

GELFOAM Sterile Sponge may serve as a nidus for infection and abscess formation and has been reported to potentiate bacterial growth [19; 30]. When Gelfoam was used in laminectomy operations, multiple neurologic events were reported, including but not limited to cauda equina syndrome, spinal
stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, and impotence [20]. Even in an enclosed space, Gelfoam also expanded and compromised the spinal cord [21-24].

In the manufacturers IFU is stated, that it is usually absorbed completely within four to six weeks. But as previously described residual hemostatic material might not be resorbed in the time given from manufacturer (Figure 2, Gelfoam was not resorbed and still present after 3 months) and giving trouble in postoperative diagnostics, e.g. mimicking tumors [8]. As described above these hemostats (here Surgicel, Oxycel, Avitene and Gelfoam; [8]) may produce significant space-occupying mass lesions appropriately termed textilomas that are clinically and/or radiologically apparent. Textilomas may present with neuroimaging features that mimic recurrent tumor.

Notable: In 2004 the FDA released notification to users about Gelfoam® and its swelling and use in neurosurgical procedures because of the potential for paralysis.

Giant cell granuloma has been reported at the implantation site of absorbable gelatin product in the brain [21], as has compression of the brain and spinal cord resulting from the accumulation of sterile fluid [25]. Foreign body reactions, “encapsulation” of fluid and hematoma have also been reported [19, 27]. The ability of Gelfoam of fluid absorption and late swelling when left in place as a hemostatic cover in a resection field it causes it might cause severe adverse events. Gelfoam was the active agent in the case below (Fig. 3) [27]. This is consistent with many reports on granulomas caused by that material. Excessive fibrosis and prolonged fixation of a tendon have been reported when absorbable gelatin products were used in severed tendon repair. Fever, failure of absorption, and hearing loss have been reported in association with the use of GELFOAM sponge during tympanoplasty [19].
Fig. 3: MR image revealed a ring-enhancing structure (arrow) that was believed to be recurrent tumor leading to reoperation 2 months after first operation. A glasslike mass with the macroscopic appearance of Gelfoam was resected (arrow) [27].

In 1999 a new agent was introduced called Floseal™ which basically consists of thrombin plus cross-linked gelatin granules mixed together. Bovine based devices bears the risk of transmissible diseases. So the way it works is your bovine thrombin directly activates fibrinogen and converts it into fibrin monomers. Of note, Floseal™ do cause more inflammatory reactions than the others. Floseal™ does require two to five minute prep time, you combine the thrombin with calcium and combine that to the gelatin granules. The completely mixed product has to be used within 2 hours. Floseal™ should not be used in combination with blood salvage or cardiopulmonary bypass systems. Floseal™ is much more expensive than the others.

**CARBOXYMETHYL STARCH PRODUCTS:**

Starsil Hemostat is a Carboxymethyl-Starch powder that will be CE-marked in 2012. It is a second generation starch based product with more water-absorption capacity and more efficacy regarding the hemostatic effect, when compared to the starch powders of the first generation like Arista MPH.

Starch based hemostat powders have a broad range of application and good hemostatic effect. To date, there are no serious product related adverse events known. Even more, there is evidence that starch powder might prevent adhesions [28]. Hoffmann and coworkers [28] proved in a rat cecal model that Carboxymethyl starch particles do not enhance inflammation. They tested six agents: Starch particles, glutaraldehyde activated collagen, thrombin coated collagen microspheres, thrombin activated fibrin polymer, polyethylene glycol polymer and oxidized cellulose. In the histopathological examination of rat caecum the Starch particles and polyethylene glycol polymer demonstrated significantly lower adhesion formation than controls and others and some even aggravates inflammation and foreign body reaction.
There are numerous articles published which are dealing with starch based hemostatic powders. All hemostatic products like Surgicel, Gelfoam, Floseal or even Starch based powders have an ability for adverse events like granuloma formation, inflammation, foreign body reactions or blockade of healing. But these reactions are less distinct with starch powders [29]. The degradation process of Starch particles is enzymatically performed by Amylase and Pyrase. Thus, there is only mild or no foreign body reaction [28]. Another study demonstrates that Starch powders do not enhance abdominal infection like various Gelatin products [30]. In the animal study of Ereth and coworkers an animal infection model demonstrates this (Fig. 4+5).

Microporous Polysaccharide Hemospheres do not enhance abdominal infection in a rat model compared with gelatin matrix.  

Colony Forming Units of E.Coli 72 hr post inoculation in rat abdominal wounds  

Fig. 4+5: Starch powders like Starsil (here MPH) do not enhance abdominal infection, but gelfoam does. When Gelfoam was used in presence of E.coli the colonization rate “exploded” significantly after 72 hrs.
Mode of action of Starsil® Hemostat:
The hydrophilic polysaccharide spheres are synthesized by cross-linking purified plant starch and do not contain any human or animal components. The carboxymethyl starch (CMS) particles functions as molecular filters by separating serum from the cellular constituents such as platelets and erythrocytes. The CMS particles are a fine white and sterilized powder which is filled in a 1 to 5 g bellow bottle. If necessary an applicator is attached to access difficult to reach wound areas. This gives more credit to starch powders when used for minimal-invasive surgery, because it is much easier to reach. The application of some hemostatic or products that prevent adhesion formation is often difficult. Especially fleeces, textile based products or membranes are difficult to apply through the laparoscopic channel and they are often difficult to handle [30]. Starch powders like Starsil are easy to apply through a scope using an applicator. They are not limited to any region. Other products like e.g. Seprafilm, Gelatin fleezes are not very easy to handle, and experience is needed to apply the product as intended. E.g. dislocation of the membrane or fleezes might be possible after application, and this may diminish the anti-adhesive effect [32]. Even more, dislocation might cause delirious adverse events as earlier described! Devices that would be easier to handle would probably be more effective. Especially in laprascopic surgery the Starch powder dominates with easy and fast application.

The Starch particles absorb much of the water portion of the blood and expands multiple times of its dry volume. This process acts to concentrate blood solids that are excluded, which then form a gel matrix. The gel matrix slows blood flow and serves to enhance clotting. The mesh of carboxymethyl starch particles and blood particles form a plug which acts as an temporary mechanical barrier. It is enzymatically absorbed within 72 h by degradation from alpha-amylase and pyrase. These particles are biocompatible, non-pyrogenic.

Even more compression and damage of tissue, e.g. nerves with consecutive palsy is not described with Carboxymethyl Starch powders. Starch particles acts within seconds and after its use in surgery and closure of the wounds, there is no late swelling like it is described with Gelatins sponges or Oxidized cellulose.

**Conclusion:**
Starch powders like Starsil are a further development of medical devices for hemostasis in surgery. It can be used in all kind of surgical procedures (only ocular surgery with open chamber or open vitreous body is excluded). To date, no major product related adverse events were reported. In contrast there exist already a large number of trials or case reports which demonstrates negative effects of other hemostatic devices like oxidized cellulose or Gelatin based sponges and matrix (with or without Thrombin). This limits the use of these devices for some surgical indications.
Literature:


[19] IFU Gelfoam® (abssorbable gelatin sponge, USP) and Gelfoam® Plus Hemostasis Kit


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AMENDMENT TO THE ARTICLE FROM SEPTEMBER 20TH, 2011:

“Comparison of Topical Hemostatic Agents: Starch powder, Gelatin sponge or Gelatin matrix and Oxidized regenerated Cellulose
Review of Adverse Events”

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STARSIL Hemostat is a Carboxymethyl-Starch powder that was CE-marked in 2012. It is a second generation starch based product with more water-absorption capacity and more efficacy regarding the hemostatic effect, when compared to the starch powders of the first generation like Arista MPH. The device is ready to use and needs no preparation and has a broad range of use in surgical procedures (Fig. 1). There are studies published or submitted for publication demonstrating the efficacy and safety of STARSIL Hemostat in open surgery or minimal invasive laparoscopic surgery [1-4].

To date, over 40 000 units of Starsil were sold. There are no serious product related adverse events reported. In contrast, there are many more articles in the literature presenting adverse events and side effects with the use of oxidized cellulose or Gelatin-based products as shown above (Review from September 20th, 2011) or demonstrated below (Fig. 2 and 3) [5-8]. As previously published, we did not observe any severe adverse events resulting from Granuloma formation, inflammation, foreign body reaction enhancement of infection, compression of nervous structures or brain resulting in palsy or paraplegia, occlusion of vessels or bypass-grafts. With use of Starsil in minimal invasive laparoscopical gynecological procedures the surgeons were very satisfied with bleeding control [2]. With the applicator the powder was very easy to apply and in addition an adhesion preventive effect is assumed. Same satisfying observation was as well found in all kinds of surgery, like neurological-, orthopedic-, abdominal-, cardiac surgery [1]. In abdominal surgery a study was performed to demonstrate good to very good effect of bleeding control and in addition adhesion prevention with STARSIL [3]. An interesting observation was made in plastic and reconstructive surgery, where skin transplantation after heavy burns was found to improve attachment and healing [4]. All surgeons were very pleased with the easy application and good to very good bleeding control even under difficult conditions.
Fig. 1: Some examples for the use of Starsil Hemostat in different surgical settings ranging from cardiac surgery, general surgery, abdominal surgery, trauma surgery, orthopedic surgery, plastic and reconstructive surgery or gynecological and laparoscopic surgery
Fig. 3: Persistence of combined use of three “absorbable” hemostatic agents (“package” of Surgicel, Floseal and Tissel; arrow) applied during laparoscopic nephron-sparing surgery for renal cell carcinoma (A= CT-scan 3 months postop). Follow up CT-scan (B) 1,5 years later shows still presence of the “hemostat-pack” (arrow) [5].

Fig. 4: Surgicel applied during laparoscopic cholecystectomy. A= CT-scan on postop day 4 with some air bubbles (white arrows). CT-scan 5 days later demonstrates increase in size of the region compatible with development of an abscess (white arrows) [5].

Munich, January 5th, 2016
Dr. med. Helmut Mair
Literatur:


