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REVIEW

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# The use of local agents: bone wax, gelatin, collagen, oxidized cellulose

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**Abstract** The use of local agents to achieve hemostasis is an old and complex subject in surgery. Their use is almost mandatory in spinal surgery. The development of new materials in chemical hemostasis is a continuous process that may potentially lead the surgeon to confusion. Moreover, the more commonly used materials have not changed in about 50 years. Using chemical agents to tamponade a hemorrhage is not free of risks. Complications are around the corner and can be due either to mechanical compression or to phlogistic effects secondary to the material used. This paper reviews about 20 animal and clinical published studies with regard to the chemical properties, mechanisms of action, use and complications of local agents.

**Keywords** Oxidized regenerated cellulose · Bone wax · Gelatin foam · Collagen fleece · Local hemostasis

## Introduction

Hemostasis in spinal surgery requires different tools for each step. Bipolar electric coagulation allows controlling subcutaneous bleeding. Muscular dissection is often performed by monopolar electric coagulation. Hemostasis of the muscular layers is performed by bipolar coagulator and maintained by mechanical compression of spreaders. Each procedure on the bone (laminectomy, screw placement, etc.) carries the risk of conspicuous bleeding, mostly from cancellous bone. Its control is achieved by means of bone wax. The epidural phase of spinal procedures probably carries the longest and highest risk of bleeding. The explanation is that the surgical field is deeply seated, and the bleeders are usually difficult to find. Iatrogenic damage of the epidural venous plexus increases the risk of fighting against low pressure. However, continuous venous bleeding is difficult to control and time consuming. During this step, oxidized, regenerated cellulose and fibrillar collagen are very useful. The aim of this article is to review the most common topical hemostatics used in spinal surgery.

## Historical background

In the event of hemorrhage, hemostasis is naturally carried out by vasal contraction, platelets, coagulation factors and blood flow. Sometimes during an operation, it is not possible to wait for the natural hemostatic process to occur, and, therefore, additive methods to obtain a stable coagulum have to be used [11, 23, 49].

In general, these methods fall into one of the three basic categories: thermal, mechanical, or chemical means [6, 49]. The use of thermal energy to obtain hemostasis dates to ancient Egypt, and the importance of electric coagulation in neurosurgery was stated in 1920 by Cushing and Bovie [11]. Mechanical hemostasis is principally ligature, but it has been said that the feature that most distinguishes spinal microsurgery as a specialty is control of hemorrhage without ligature.

**Table 1** Topical hemostatic agents

| | Bone wax | Gelatin | Microfibrillar collagen | Oxidized cellulose/ regenerated |
|---|---|---|---|---|
| Year of introduction | 1886 | 1945 | 1970 | 1942/1946 |
| Ingredients | Beeswax, Vaseline | Purified animal gelatin | Purified bovine corium collagen | Wood pulp (oxidized regenerated cellulose) |
| Action | Mechanical on trabecular vascularization of bone | Provides physical matrix, swells | Direct platelet release stimulation, provides a surface, does not swell | Mechanical action, swells, gel formation, interaction with proteins and platelets, low pH denatures globulin and albumin |
| Absorption | None | 4–6 weeks in soft tissues | Less than 84 days in animal studies | Depends on the amount used, degree of saturation with blood and tissue bed |
| Complications | Allergic, granuloma, cord compression, infection, interferes with bone healing | Cord compression, interferes with bone healing | Interferes with bone healing, allergic reactions, infection | Cord compression, interferes with bone healing, encapsulation of fluid, foreign body reactions |

Chemical hemostasis also has a very old origin. Hippocrates used caustics to achieve hemostasis, but the history of modern chemical hemostatics began at the end of the eighteenth century, when Carnot introduced gelatin. A few years later, Horsley, an innovative surgeon, observed in canine skullsthat modeling wax was efficacious in stopping bleeding. In 1886 he developed a mixture of beeswax, salicylic acid, and almond oil, thus leaving hislegacy of "antisepticwax." He advocated the application of muscle stamps anddeep anesthesia to control hemostasis during cranial and spinal surgery [46].

Research into the mechanism of blood coagulation led to the development of oxidized cellulose in 1942 [13] and gelatin foam in 1945 [27]. Until now the hemostatics most used in neurosurgery have been oxidized, regenerated cellulose (Surgicel), gel sponges (Gelfoam, Spongostan) and collagen fleece (Avitene). Local hemostatics should be removed at the end of the operation, but these materials are absorbable and so they are often left in place to avoid postoperative hematomas. Bone wax is a mixture of beeswax (70%) and Vaseline (30%). It is a non-absorbable material, becoming soft and malleable in the hand when warmed.

Gelatin foam (GF) was introduced as a hemostatic agent in 1945 and has been marketed by the present seller since 1952 [27]. Microfibrillar collagen (MFC) was developed in 1970 by Hait [17]. It is derived from purified bovine corium. The classical form (flour form) is a water-insoluble, partially acid salt of collagen, processed into microcrystals. It is dry, fluffy, white, and self-adherent. The sheet form is a non-woven web derived from compression of the flour form.

Oxidized cellulose (OC) was introduced in 1942, whereas oxidized regenerated cellulose (ORC) was developed in 1960 and is manufactured from wood pulp, which contains about 50% cellulose by mass. In order to arrive at a purified cellulose, it has to be decomposed and then recomposed into regenerated cellulose.

## Chemical properties

Bone wax is a well-known topical hemostatic agent composed of beeswax and Vaseline. Its hemostatic effect is based on physical rather than biochemical properties: it allows clot formation by stopping the blood flow from damaged vessels into the bone (Table 1).

Gelatin foam (absorbable gelatin sponge) is made from animal-skin gelatin whipped and baked into its sponge form. Although it is derived from animals it is largely considered non-antigenic. At the end of the coagulation cascade, plasma still leaks through it. Its bond to surfaces is strong. Gelatin foam paste is derived from the parent gelatin foam. If soaked in thrombin, it directly acts on the coagulation cascade. Its effect is probably mostly mechanical on low-pressure bleeders [29].

MFC adheres tightly to bloody surfaces, with an immediate and complete hemostasis. Blood rarely leaks through it. The surfaces remain white and dry. It doesn't swell, as Gelfoam does. The hemostatic properties of MFC rely on the promotion of platelet aggregation. In vitro studies have shown that platelets adhere to MFC while undergoing normal morphological changes during the release reaction [54]. Similarly, in vivo studies have shown tight adhesion of MFC to the injured surface, with platelets tightly entrapped in the MFC. Furthermore, MFC has been shown to be effective in case of heparinization, but less effective in thrombocytopenia [1]. MFC hemostatic properties are also improved by its strong adhesion to injured surfaces: it physically blocks injured vessels. It remains tightly bound to the wound, even after hemorrhage has stopped. MFC is supposed to promote hemostasis by providing a surface to which platelets can adhere and undergo their release reaction and by accelerating clotting via direct action on platelets [2, 14, 30, 32]. Advantages of collagen fleece are fast induction of hemostasis, low

tissue reaction, and fast resorption [4] .Another significant advantage is that excess collagen can be carefully teased away from around the hemorrhage site without re-initiating bleeding. A major disadvantage of using the collagen fleece is difficulty in manipulating the agent during attempts to place it in the area of bleeding [34].

ORC is a chemically altered form of cellulose [26, 33, 48, 49]. In this form, the cellulose is first dissolved and then made into a continuous fiber. The greatest use of this material has been for the control of oozing from broad surfaces, but it can be also pressed under osteoplastic flaps to supplement bone waxing or used to stop oozing from dural surfaces. It can also be applied directly on brain surfaces, to control bleeding from small vessels [48].

Oxidized regenerated cellulose in the fibrillar form (ORMC) is not markedly different from the other Surgicel cellulose-based products currently available [26]. However, it seems to be more advantageous than the standard forms in dealing with venous bleeding and oozing from cortical surfaces after tumor resection. Additional advantages are related to the physical properties of the loosely knit, regenerated cellulose. This allows placement in certain areas where the product will rapidly conform to the recipient surface, giving a favorable three-dimensional structure for the clot organization. Oxidized regenerated cellulose also seems to confer hemostasis by decreasing the pH and acting as a caustic, thus generating an artificial clot. The clot is brownish because of the production of acid hematin [2, 26, 28]. ORC presents multiple mechanisms of action, including physical and mechanical actions in tamponade, food absorption, swelling and gel formation, and then surface interactions with proteins, platelets, intrinsic and extrinsic pathway activation.

One major advantage of oxidized cellulose is its definite and potent action against a wide variety of pathogenic organisms, both in vivo and in vitro. This beneficial effect is immediate and is exerted by a low pH effect. The current theory is that this chemical hemostatic reduces the effective initial inoculum with an acid hostile ambient, allowing the host's natural defenses to overcome the organism[49]. This has been confirmed by Spangler et al., who examined the antimicrobial effect of ORC against antibiotic-resistant organisms. ORC products were challenged with ATCC reference strains and clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), vancomycin-resistant *Enterococcus* (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and non-resistant ATCC strains of *S. aureus* and *Pseudomonas aeruginosa*. Antimicrobial activity was seen with all three ORC products against the challenging organisms. Data indicate that antibiotic-resistant microorganisms remain susceptible to the antimicrobial activity of ORC. Since low pH affects a relatively broad spectrum of bacteria and does not act in a mechanism-specific manner, as do antibiotics, antibiotic-resistant strains of bacteria are unlikely to resist the ORC pH effect. Results of this in vitro assessment support the hypothesis that the antimicrobial activity of ORC is effective against antibiotic-resistant microorganisms. Moreover, an advantage of oxidized cellulose as compared to microfibrillar collagen, from the standpoint of infection, has been suggested [43]. Oxidized cellulose has previously been shown to be superior to gelatin sponge with respect to infection [38].

Platelet activation and aggregation play an important role in hemostasis. Topical hemostatics may interfere with platelet function. Five topical hemostatics (collagen fleece, bone wax, bioerodible polyorthoester, oxidized cellulose and gelatin sponge) have been investigated concerning their effect on platelet cascade. Fibrillar collagen fleece induced aggregation in the presence of a small amount of ADP and adrenaline. Bone wax needed a larger concentration of agonists to achieve the same result. In fact, GF, OC and polyorthoester did not promote platelet aggregation [41].

Masova et al. studied the effect of OC on platelet activation. As a marker of platelet activation they used serotonin release reaction. Serotonin release in platelet-rich plasma incubated with various concentrations of oxidized cellulose (0.5–2.0%) started in about 20 min. Washed platelets were not directly activated by oxidized cellulose within 1 h. Washed platelets reconstituted in plasma obtained from two patients with deficiency in coagulation factor XII were activated by oxidized cellulose with a prolonged lag phase. Their results demonstrate the significant influence of factor XII on blood-platelet activation by oxidized cellulose [28].

## Use suggestions

Bone wax

Use it only if necessary and just for the time needed to achieve hemostasis. After hand manipulation, a bath in iodine is recommended. If the wax is left in place, we strongly recommend meticulously removing the excess. It should never be left in place in fusion sites and within the spinal canal. It must never be used in contaminated fields.

GF

Gelfoam sponge is widely used to fill the cavity of a laminectomy in a bloody field. Attention should be paid to removing the excess, and the surgeon should be aware that GF could interfere with bone healing. In infected spaces it is contraindicated, because it may enhance the infectious process. We suggest placing it dry with moderate pressure on the bleeding site. This agent can double in volume by swelling and can also cause compressive complications. If soaked in thrombin, GF has an increased hemostatic action.

**Table 2** Clinical studies (*GF* gelatin foam, *MFC* microfibrillar collagen, *CF* collagen fleece)

| Author | Year | Clinical material | Hemostatics | Conclusion |
|---|---|---|---|---|
| Taheri | 1971 | Anterior cervical procedures | GF paste | No differences concerning bone healing compared with the patients previously treated without GF paste |
| Harris | 1978 | Total hip replacement | GF paste, GF sponge + bovine thrombin, MFC | No difference was found in terms of bone healing in the three groups of patients |
| Weiss | 1980 | Anterior cervical procedure | GF paste | See Taheri |
| Rengachary and Manguoglu | 1980 | Cloward procedures | GF paste + bovine thrombin | Good results without any allergic reaction |
| Silverstein | 1981 | Liver lacerations and retroperitoneal bleeding | Loose vs compressed CF | Partially compressed CF is an effective topical hemostatic when compressed against the bleeding site and when folded and sutured against it |
| Zirna | 1987 | Foot surgery | Bone wax, GF paste | Reduction of postoperative edema and pain |

ORC

Never use this soaked in thrombin. The latter, in fact, interferes with its natural action. Its power is maximal if applied dry; the fibrillar form when placed in small layers is almost transparent, so that bipolar coagulation trough it will still be possible. Bacteriostatic properties of this product should be preferred in particularly contaminated fields. Obviously, should this event occur, the use of no agent at all is always better. Wadding or packing in rigid cavities (neural foramina) should be avoided, due to risks related to swelling phenomena.

MFC

This should be applied dry with clean and dry instruments, and pressure with gloved fingers should never be placed, as the MFC would adhere to the glove more than on the hemorrhage site.

Postoperative adhesion of the hemostatic agent to neural structures is possible. Therefore, it is recommended to tease away the excess of product after 5–10 minutes. Swelling occurs, although less so than with other products, and surgeons should be aware of this when MFC is left in place in rigid compartments.

## Clinical studies

Because GF is resorbable in the human body, the paste form represents an alternative to bone wax to avoid osteogenic inhibition. Taheri and colleagues used powdered gelatin foam in over 300 anterior cervical procedures, applying it on the interbody drill hole during drilling. Follow-up X-ray films showed no differences concerning bone healing with the patients previously treated without Gelfoam paste [44]. Weiss also used the same agent in anterior cervical fusions, achieving excellent results [50]. Rengachary and Manguoglu added bovine thrombin to the Gelfoam paste during Cloward procedures, without any allergic reactions to the thrombin [35]. Harris and colleagues presented a series of 45 patients operated on for total hip replacement. They applied Gelfoam paste, Gelfoam sponge plus bovine thrombin, or microfibrillar cellulose on bleeding cancellous bone surfaces of femoral osteotomies. They found bleeding reduced by, respectively, 85%, 75% and 47%, over a 3-min. interval. No difference was found in terms of bone healing in the three groups of patients [18] (Table 2).

Zirna at al. compared GF paste and bone wax for their effects on the occurrence of postoperative edema and pain in foot surgery. They found that 80% of patients treated with bone wax and 91% of patients receiving GF paste presented decreased amount of postoperative edema. Furthermore, postoperative pain was reduced in 90% of the patients treated with bone wax, and in 75% of patients treated with GF paste [53].

Silverstein et al. used GF in 21 patients with liver lacerations and retroperitoneal bleeding. They tested two forms: loose and compressed fleece. Partially compressed GF showed significantly higher hemostatic efficacy than the loose form. Their clinical experience was also confirmed by gravimetric determinations of blood loss in dogs. They concluded that partially compressed GF was an effective topical hemostatic when compressed against the bleeding site and when folded and sutured against it [40].

## Animal studies

Bone wax is known to inhibit bone healing and osteogenesis. Howard and Kelley evaluated the effect of bone wax on bone healing in Albino rats. They made bony lesions in animal tibia. In the first group, the holes were filled with bone wax and then irrigated with saline solution. In the second group, the holes were simply irrigated with saline solution. After the animals were killed, the investigators

**Table 3** Animal studies (*MFC* microfibrillar collagen, *GF* gelatin foam, *ORC* oxidized regenerated cellulose, *OC* oxidized cellulose)

| Author | Year | Model | Hemostatic | Conclusion |
|---|---|---|---|---|
| Geary and Frantz | 1950 | Rib fractures in dogs | Bone wax | Fracture union was prevented by interposition of wax particles |
| Howard and Kelley | 1969 | Tibial lesions in albino rats | Bone wax | The use of bone wax should be contraindicated in surgical procedures requiring bone fusion |
| Brightmore | 1975 | Sternotomized goats | Bone wax | Bone wax causes absorption of cancellous bone and inhibits osteogenesis |
| Rybock | 1977 | Suction-evacuation lesions of canine cortex | MFC, GF | MFC appears to be as good or better than GF |
| Johnson and Fromm | 1981 | Iliac crest cancellous bone of rabbits | Bone wax | Bone wax significantly reduces the ability of cancellous bone of rabbits to clear bacteria |
| Wilkinson | 1981 | Surgical bone lesions in rabbits | Bone wax, GF | Gelatin foam paste is a good alternative to bone wax for the control of bone bleeding, and it seems not to impair bone healing |
| Ibarrola | 1985 | Experimental defects in both tibias of rats | Bone wax, cellulose, GF | All materials inhibited healing when left in situ. Bone wax inhibited osteogenesis. Cellulose reduced bone repair and caused inflammation. GF was completely resorbed, and healing was complete at 120 days |
| Alberius | 1987 | Cranial bone lesions in rabbits | Bone wax | Bone wax markedly impairs bone regeneration |
| Voormolen | 1987 | Cerebral lesions in rabbits | MFC, ORC | MFC establishes hemostasis faster, and it is resorbed faster than ORC |
| Haasch | 1989 | Osseous defects created in rat tibias | MFC | MFC doesn't impede bone healing |
| Finn | 1992 | Surgical defects in iliac crest of dogs | Bone wax, GF, ORC, MFC | MFC, ORC, and GF may be adequately used in iliac bone procurement, whereas bone wax seems to be contraindicated |
| Raccuia | 1992 | Rat model employing a standardized renal injury | OC, MFC, positively charged collagen, fibrin glue | MFC is the best overall hemostatic agent in microvascular surgery |

found that bone wax almost completely inhibited bone healing. They suggested that the use of bone wax should be contraindicated in surgical procedures requiring bone fusion [19]. Brightmore found that bone wax formed a physical barrier to bone healing in sternotomized goats, causing absorption of cancellous bone and inhibiting osteogenesis [7]. Geary and Frantz studied experimental rib fractures in dogs. They found that fractures treated with bone wax allowed the formation of the same amount of calcified callus as untreated lesions, but fracture union was prevented by interposition of wax particles in the first group. Furthermore, they noted a foreign reaction to bone wax, with monocytes, giant cells and phagocytes [15] (Table 3).

Effects of bone wax on bacterial clearance have been studied by Johnson and Fromm. They penetrated iliac crest cancellous bone of rabbits, with or without *Staphylococcus aureus*, followed by placement of a cylinder of bone wax or stainless steel rod. The site of inoculation was excised and cultured 10 days later. A positive culture was found in 80% of animals whose bone was implanted with bone wax and bacteria, and in 40% of animals with steel rod and bacteria. No positive cultures were found in the bacteria-only, bone-wax-only and steel-rod-only groups. The combination of bacteria with a foreign body created by bone wax or a steel rod was significantly different from the other groups, showing that bone wax significantly reduced the ability of cancellous bone of rabbits to clear bacteria [24].

Larocca and Macnub used GF sponge as a scaffolding for fibroblasts over a laminectomy site in dogs [25]. Wilkinson and colleagues studied GF paste's effect on bone healing and osteogenesis in 1981. They evaluated either the hemostatic or osteogenic effects on surgical bone lesions in rabbits of both gelatin paste and bone wax. Thirty rabbits received four trephine craniotomies and four lumbar laminectomies, alternatively treated with either gelatin paste or bone wax. The mean intraoperative blood loss was similar in both groups. At 1 week postoperatively, histological examination of the fracture site showed no differences, but at 4 weeks only the gelatin-treated site specimens were satisfactorily processed with new bone formation and no foreign body reaction. At 6 weeks, the force required to fracture the bone at the trephination sites was similar for both groups. They concluded that gelatin foam paste is a good alternative to bone wax for the control of bone bleeding and that it seems not to impair bone healing [51].

The effects of bone wax, cellulose and gelatin on bone healing were microscopically evaluated by making exper-

imental defects in both tibias of rats. Hemostatics were placed and left in situ in the right tibias, whereas they were removed after 10 min. from the left side. All three materials inhibited healing when left in situ. Bone wax inhibited osteogenesis. Cellulose reduced bone repair and caused inflammation. Gelatin was completely resorbed and healing was complete at 120 days [20]. MFC did not impair bone formation in rat tibias in the Haasch study of 1989 [16]. Alberius et al. studied the effect of bone wax on rabbit cranial bone lesions. The lesion rim covered by bone wax presented a slight tissue reaction and a markedly impaired bone regeneration [3].

In 1987, Voormolen et al. conducted an experimental study in rabbits in which cerebral lesions were made and filled with oxidized regenerated cellulose (not in fibrillar form) and collagen fleece. In this study, bleeding times were evaluated and histological studies were realized. Results showed lower bleeding times for microfibrillar collagen, with a quicker resorption rate than for traditional oxidized regenerated cellulose. Voormolen concluded that collagen fleece established faster hemostasis than oxidized cellulose and that it was resorbed faster than oxidized cellulose [48].

Rybock et al. compared hemostatic properties of MFC versus GF in suction-evacuation lesions of the canine cortex. MFC was found to be faster and more effective than GF in achieving hemostasis. Histological evaluation at 2 months, 4 months and 6 months postoperatively didn't show any difference in regard to the amount or type of tissue reaction to the two agents. They concluded that MFC appeared to be as good as, or better than, GF, because it is absorbable; doesn't lead to major tissue reaction; doesn't swell significantly; and is quickly effective even in the presence of coagulation disorders. Also, smaller quantities of MFC remain in the wound after excess material is removed [37].

Wagner in 1996 quantitatively compared six commonly used topical hemostatic agents in terms of their ability to mediate platelet aggregation, deposition and activation in a series of in vitro tests. He presented an overall activity ranking of the materials used: collagen>gelatin>oxidized regenerated cellulose [49]. The efficacy of four topical hemostatic agents (oxidized cellulose, microfibrillar collagen powder, positively charged modified collagen and single donor heterologous fibrin glue) was compared in a rat model employing a standardized renal injury. Fibrin glue was by far the most effective agent in controlling hemostasis. The collagen materials, though effective, required a longer time to control bleeding and did not differ from one another statistically in their activity. Microfibrillar collagen was showed to be the best overall hemostatic agent in microvascular surgery [34].

It has been shown that Avitene does not impede bone healing in osseous defects created in rat tibias. MFC, bone wax, GF and ORC were compared by Finn et al., concerning their effects on osseous regeneration. They researchers made surgical defects in the iliac crest of four dogs. Two months later, radiographic and histologic examination showed new bone formation in the presence of MFC, ORC, and GF. Residual material incorporated in bone was noted in MFC and GF sites. Bone wax showed a marked foreign-body reaction and lack of bone reformation. They concluded that MFC, ORC, and GF might be adequately used in iliac bone procurement, whereas bone wax seems to be contraindicated [12].

## Complications

Most complications are due to mechanical compression of neural structures, due to the blind application of local agents into closed bone compartments or due to the natural swelling of those products. Other complications are sustained by the antigenic action of those products, which even if with a low rate, are possible. Bone healing is always slowed by all the reported hemostatics.

Brodbelt et al. presented three cases of paraplegia after thoracic surgery during which ORC had been used during thoracotomy for hemorrhage control. The ORC was later found to have passed through the intervertebral foramen, causing spinal cord compression. They stated that in all intraspinal and perispinal procedures, the over-liberal use of ORC should be avoided, and attempts made to remove all excess ORC once adequate hemostasis is obtained [8]. Iwabuchi first, and later Cherian, have reported similar cases in 1997 and 1999 [9, 21]. The manufacturer warns of encapsulation of fluids.

Bone wax is known to cause adverse effects such as allergic reaction, intracranial granuloma, epistaxis, and granulomatous infection. A case of iatrogenic quadriplegia has been reported by Cirak. In this case neurological deficit might have been caused by either direct compression from bone wax or by epidural bleeding by detachment of epidural veins [10].

Katz and colleagues reported two cases with bone wax granulomas of the orbit as a remote surgical complication in a large orbital surgical series. In one case, intraoperative cultures grew *Staphylococcus aureus*, showing that bone wax may act as a nidus for infection [22]. Seven cases of bone wax granuloma have been reported in women who underwent foot surgery. At re-operation, soft granulation tissue was resected. Microscopically, in all cases, a marked foreign body reaction was seen [5]. Sorrenti et al. found a definite foreign-body giant cell reaction to bone wax in 12 patients treated by elevation of the tibial tubercles. Giant cells eliminated bone wax particles from the site, culminating in a fibrous reaction [42].

Verborgt reported a case of a retroperitoneal tumor as a late complication of the use of bone wax in harvesting iliac crest. The tumor needed surgical removal 19 years later. Microscopically, a bone wax granuloma was diagnosed [47]. Wolvius reported a case of foreign body granuloma in a cranial defect [52].

Robicsek et al. used radioactive bone wax on the cut sternum. There was evidence of radioactive material in peripheral lung, indicating that bone wax may embolize. They concluded that embolization occur in clinical conditions and may give rise to secondary pulmonary complications [36].

In order to avoid bone wax complications, alternative materials have been developed. Orgill et al. reported their experience with a polyethylene glycol/microfibrillar collagen composite (PEG/MFC) that has inherent hemostatic qualities, is biodegradable, and is compatible with bone repair. The composite was placed in cranial defects of New Zealand white rabbits. Hemostasis and healing were compared to unfilled defects and defects filled with bone wax. Both PEG/MFC and bone wax stopped bleeding. The former was resorbed in 8 h, and the microfibrillar collagen was resorbed over 2 months, eliciting only a minor inflammatory response during the first month. Defects filled with the PEG/MFC composite showed similar amounts of bony regeneration, as did unfilled control defects. At 4 weeks, healing bone accounted for 43%, (+/-13%) in those treated with PEG/MFC and 47% (+/-19%) defect area in untreated holes. By contrast, less than 1% of the area was bone in defects filled with bone wax. They concluded that PEG/MFC composite provided excellent bony hemostasis and did not inhibit bone growth [31].

An experimental, biodegradable polymer ceramic composite combined with recombinant human transforming growth factor beta (rhTGF-beta 1) has been presented by Schmitt and colleagues. The polymer/rhTGF-beta-1 combination was introduced into calvarial defects in rabbits to evaluate biodegradability, biocompatibility, hemostasis control, and bone promotion. Evaluations consisted of clinical examinations, standardized radiography, radiomorphometry, as well as histology and histomorphometry. Radiomorphometric data indicated that standard-size defects treated with the wax-like polymer alone and the polymer plus 2.0 µg of TGF-beta 1 were significantly more radiopaque than control sites at both 6 weeks and 12 weeks. Histomorphometric data revealed that the amount of new bone was significantly greater at 6 weeks in the polymer plus 2.0 µg of TGF-beta 1 and in the control group than in the polymer alone. Moreover, at 12 weeks, there was significantly more new bone in the control than in either the polymer alone or the polymer plus 2.0 µg of TGF-beta 1. They speculate that the incomplete biodegradation of the polymer ceramic composite contributed to the radiopacity and may have retarded osseous regeneration. The bone-wax-like polymer material was biocompatible and acted as a hemostatic agent [39].

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. Toxic shock syndrome has been reported in association with the use of Gelfoam in nasal surgery, as warned by the producer.

MFC is of bovine origin and capable of producing a variety of allergic reactions. It has no bacteriostatic properties and can enhance an infection. It interferes with normal wound healing of soft tissue and bone. Therefore, it should be removed from the site of application before closing. It is believed to increase adhesion formation around neural structures. Its swelling rate is lower than other hemostatics; but it still occurs, so compression complications could also happen.

## Conclusions

Local agents are largely used to reduce blood loss in spine surgery. Although many new materials are presented each year, the best hemostatic agents have been the same for several decades. Using local agents for chemical hemostasis is not free of risk of complications. Consequently, the spine surgeon should be aware of these and choose the appropriate product for each procedure, following directions for use and using only if strictly necessary.

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