Chapter

Biosurgical Materials in Neurosurgical Applications: From Pioneers to Leaders

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Abstract

Hemostasis in neurosurgery has evolved significantly over the past few decades. New advances in hemostatic agents, some developed specifically with neurosurgical applications in mind, allowed for more effective control of difficult intraoperative bleeding. These agents vary in the mechanism of action and each may be indicated in different and often highly specific situations. Here we present a review of the most commonly used hemostatic agents, their mechanism of action and their indications. Focus is placed on key aspects and considerations regarding the use biosurgical materials in neurosurgery, with emphasis on clinical appropriateness and patient safety.

Keywords: biosurgery, biosurgical hemostat, biosurgical materials, hemostasis, neurosurgery, surgical bleeding

1. Introduction

The popularization of general anesthesia by William Morton in the 1840's and the concept of antisepsis introduced by Joseph Lister would lead to a paradigm shift and the emergence of modern surgery [1, 2]. The mastery of surgery was no longer associated with speed or flamboyance, but instead focused on meticulous dissection, careful handling of tissues, hemostasis, and correct approximation of tissue planes to promote adequate healing. Among operative specialties, this transition from "art" to "science" of surgery was most profound in the neurosurgical field, enabling rapid advances to occur.

Early in the evolution of modern surgery, the issue of hemostatic control became prominent, as the heavily vascularized central nervous system and its propensity to bleed resulted in limitations of procedures and posed significant challenges [3–5]. Surgical ligation was utilized sparingly for fear of vessel rupture or vascular occlusion that may compromise entire vascular distributions. The instruments and techniques in neurosurgical armamentarium therefore relied predominately on application of pressure with gauze to combat bleeding [3, 6]. As a result, a search and incorporation of novel alternatives in hemostatic techniques would effectively lead to the development of modern neurosurgery as represented by Horsley's use of bone wax and other pioneering hemostatic maneuvers [7, 8] and the introduction of electrosurgery by Cushing and Bovie in the 1920's [9, 10]. Later in the revolutionary era of neurosurgery, biosurgical materials were introduced [6, 11].

2. Neurosurgical biosurgery

In its broadest sense, the term biosurgery relates to the utilization of biomaterials that are defined as systemically and pharmacologically inert substances designed for implementation within or incorporation with living systems [12–14]. In the context of the current chapter, biosurgical materials (BSMs) are defined as biomaterials that are intended as adjuncts in attaining surgical hemostasis [15, 16]. The gradual development of hemostatic techniques has greatly impacted not only the field of neurosurgery, but all of surgery. The application of biosurgical agents first developed in the neurosurgical theater proved immensely valuable across virtually all surgical applications.

One of the earliest neurosurgical applications of biosurgical hemostats involved the control of bleeding in inaccessible areas with difficult tissue topography and in situations where use of electrocautery, sutures, or clips may simply not be feasible [4, 13, 17]. This chapter will review the categories, mechanism of action, efficacy, advantages, disadvantages, and complications of the various biological materials currently available for hemostasis in neurosurgery.

3. Classification

The abundance of biosurgical materials available for use requires a system of categorization. These agents can be divided into specific categories based on their mechanism of action, including passive or active hemostatics, flowable agents, and sealants [18–20]. Passive or mechanical agents act through contact with the site of bleeding to promote platelet aggregation [21, 22]. They form a matrix type network at the site of bleeding, thereby activating the coagulation pathway to provide a platform for platelet aggregation and clot formation. At the same time, these agents will be ineffective if used on patients with known coagulopathies due to factor deficiencies or platelet dysfunction. These products include gelatins, collagens, cellulose, and polysaccharide spheres. They require no special storage, minimal or no preparation, and are relatively inexpensive [23, 24].

Active hemostatic agents act biologically and directly participate in the coagulation cascade to stimulate fibrinogen at the site of bleeding to produce a fibrin clot [21, 25]. These agents primarily include the different forms of thrombin, and are useful in patients with coagulopathies or platelet dysfunction [18, 26]. However, they rely on the presence of fibrinogen in the patient's blood to be effective. In general, they control bleeding more effectively than passive agents, are more costly, and are prepared/available in various forms and formulations.

Flowable hemostatic agents consist of various combinations of active and passive components within a single application [20, 27]. This category includes products that work by providing a physical barrier to blood flow while actively converting fibrinogen in blood into fibrin at the bleeding site [26, 28]. Finally, sealants work by the formation of a barrier impervious to flow [24, 29]. There are several types of sealants currently available for use. Our subsequent discussion will focus on each of the various types of biosurgicals utilized, with emphasis on neurosurgical applications.

4. Passive hemostatic agents

4.1 Microfibrillar collagen

This material contains 1-μm microcrystals of purified bovine dermal collagen available as flour-like or sheet-like format [30, 31]. The microcrystalline collagenous

network provides surface for platelets to aggregate while coagulation factors are released [30, 31]. The effectiveness of microfibrillar materials may be decreased in cases of severe thrombocytopenia (<10,000 mL) [32]. The material should be kept dry prior to use because moisture may decrease its activity and the hydrophilic nature of product results in adherence to surgical gloves and possible misapplication. Consequently, the material is best handled with sterile forceps. As with other biologic hemostats, optimally the smallest amount required to arrest bleeding should be utilized, although this may not be precisely known in every situation.

Of importance, microfibrillar collagen is considered a foreign substance and can therefore serve as a nidus for infection and/or foreign body reaction [33]. The small particles of the flour-like material are useful for arresting bleeding from cancellous bone. In this setting, it has demonstrated superior efficacy when compared with other agents, such as thrombin alone or thrombin combined with gelfoam [7]. It also does not seem to interfere with bone healing in contrast to oxidized cellulose or bone wax [34]. It is recommended to firmly pack product into bone surface followed by direct pressure for 5–10 minutes. In terms of clinical application considerations, it should not be used in areas where it may exert pressure on adjacent structures because of fluid absorption and expansion. Also, excessive expansion along a dural sinus may lead to occlusion after bone flap replacement. Although collagen is relatively less antigenic and only results in minor inflammation there remains the very small risk of allergic reactions [35, 36]. Finally, it can also lead to infection, abscess, pseudo-abscess or granuloma formation [37–39].

4.2 Oxidized regenerated cellulose

This type of biomaterial was developed in the 1940's to help facilitate hemostasis [40, 41]. It is available as pads, strips or powder [40, 42, 43]. It can absorb seven to ten times its own weight [44]. This ubiquitous hemostatic agent is one of the most frequently used. Upon contact with blood, the material reacts to form a reddish black gelatinous mass containing hematin (accounts for the color change) [45]. The oxidation of cellulose results in a product of low pH with resultant bacteriostatic properties [46, 47]. Despite the antimicrobial properties the rates of infection do appear to correlate with the amount of retained product [48]. Consequently, though often left in place in surgical beds, excess amounts should be removed prior to wound closure. Of note, the addition of saline or thrombin to oxidized regenerated cellulose may decrease its effectiveness in addition to inactivating thrombin as a result of the acidic environment [49]. It may also interfere with bone healing and may cause blood vessel compression [49]. Finally, there are reports of excessive postoperative swelling of this type of biomaterial [50].

4.3 Absorbable gelatin sponge

Also introduced in the 1940's this type of hemostatic material consists of water-insoluble sponges prepared from purified porcine skin gelatin [11]. It provides hemostasis by absorbing up to 45x its weight in fluid, thus restricting blood flow and providing stable matrix for clot formation [51]. Gelfoam with gentle pressure can tamponade and treat most dural sinus bleeding without occlusion of the sinus. Although hemostatically beneficial, this capacity to expand physically can lead to compression of neural (and vascular) structures [52]. Absorbable gelatin material is considered relatively nonreactive, however there have been case reports of giant-cell granuloma formation at the implantation site [53, 54]. Although generally non-antigenic, this type of biosurgical material is considered a foreign body and can serve as a nidus for infection [55].

4.4 Polysaccharide hemospheres

This is a relatively new category of biosurgicals, derived from vegetable starch containing no animal or human components [56–58]. It is available in powder form with a bellows-type applicator [56, 59]. The material requires no mixing and is available for immediate use. It produces a hydrophilic effect to dehydrate blood and concentrate solid components to increase barrier formation [59, 60]. It poses little risk to patients since it lacks any human or animal components and should not be used in closed spaces because of physical expansion / swelling.

5. Active hemostatic agents

5.1 Thrombin (bovine, pooled human plasma thrombin, and recombinant)

There are three forms of thrombin products differentiated based on type of plasma used to provide concentrated thrombin to rapidly convert fibrinogen to fibrin clot [61–63]. This class of biosurgicals should be used in cases of mild to moderate bleeding, mainly because such products tend to be easily washed off in the setting of brisk arterial bleeding or surgical irrigation [64]. In addition, thrombin-based hemostatic agents may be less effective in situations of severe fibrinogen deficiency [15]. Finally, thrombin products should not be allowed to enter the vascular system as intravascular thrombosis can occur [65].

Antibody formation represents a risk with the use of bovine thrombin, leading to coagulopathy and even death in rare cases [66, 67]. In fact, there is a "Black Box" warning associated with this complication. The use of bovine thrombin is contraindicated if the patient is allergic or has known sensitives to materials of bovine origin [23, 68]. On the other hand, pooled human plasma carries a potential risk of viral or prion disease transmission since multiple units of blood are required to manufacture each lot of product [69, 70].

5.2 Flowable agents

These products represent a combination of absorbable passive and active hemostatic components [71, 72]. One of the flowables currently available is a combination of bovine gelatin particles and pooled human thrombin [73, 74], while the other consist of absorbable porcine gelatin particles combined with stand-alone thrombin [27, 75]. In order to become effective, the flowables require direct contact with blood as fibrinogen source [76]. Reconstitution is required, with these products having a paste-like consistency and the ability to "remain in place" compared to liquid thrombin [43]. Flowables are applied with a syringe-like applicator and require 2–3 minutes of preparation time [28, 77]. Direct injection into emissary veins or venous sinuses should be avoided to decrease the risk of dural venous sinus thrombosis and post-operative venous stroke.

6. Sealants

6.1 Fibrin sealants/glue

This group of agents consists of concentrated fibrinogen and thrombin. They increase the rate of blood clot formation by providing higher concentrations of both fibrinogen and thrombin [78]. There are three available types: (a) Pooled human

plasma [79, 80]; (b) Individual human plasma, bovine collagen, and bovine thrombin [81]; and (c) Pooled human plasma and equine collagen [82].

Sealants may be used in coagulopathic patients with insufficient fibrinogen [64, 78, 83]. These agents can also be used in heparinized patients since they do not rely on host factors for hemostasis [84–86]. Typical indications are hemostasis during cardiopulmonary bypass, splenic injuries, and a number of less commonly utilized general surgical applications [23]. However, they are widely used as hemostatic adjuncts and sealants during neurosurgical procedures, including the prevention of cerebrospinal fluid (CSF) leaks [87, 88].

6.2 Polyethylene glycol polymers

There are three different product types in this class of biosurgicals [89, 90]. They tend to be most efficacious when used on a relatively dry field to allow sufficient time for polymerization [91]. One type of polyethylene glycol polymers (PGPs) consists of a combination of 2 polyethylene glycol (PEG) polymers that cross-link to each other and contact tissue following application [92]. In effect, the PGP-based network acts as a sealant to tissue fluids as well as barrier to cell ingrowth and adhesion formation [92, 93].

Another type of PGP material consists of a combination of PEG polymer, trilysine amine, and blue dye [94, 95]. This particular component mix produces a hydrogel able to help with dural closure because of its ability to form a watertight seal [96]. A modified derivative using a reduced molecular weight PEG component can be used in sutured dural repair during spinal surgery [96, 97]. The built-in blue dye is used to provide accurate placement of sealant [98, 99]. Some concerns about this particular material being associated with cases of postoperative spinal cord compression have been voiced [94, 100–102]. As such, specific non-expanding formulations exist for usage in the spinal canal [103].

The third class of PEG polymer compound consists of a combination with human serum albumin. This substance is biodegradable and fairly well studied in terms of safety and effectiveness [104]. It provides a strong barrier, as evidenced by the FDA approval for use on visceral pleura to close air leaks of >2 mm during pulmonary surgeries [105]. There may also be associated economic benefits of using this type of biologic sealant [106].

7. Neurosurgical applications

It is important to realize that biosurgical agents are adjuncts to hemostasis when standard methods like direct pressure, suturing, or cautery are impractical or ineffective [107, 108]. Good knowledge of the mechanism of action of different available biosurgical hemostats is critical, with multiple considerations including the patient's anticoagulation status, the rate of bleeding, the presence of thrombocytopenia, fibrinogen level assessment, and many other factors. The choice of a specific biosurgical product should be dependent on the type of surgery, site of bleeding, other anatomic considerations, cost, and preference of the operating neurosurgeon [3, 16, 32, 109, 110].

The continuous oozing encountered from dilated varicose intraspinal veins and bone during spinal surgery can be effectively managed with topical hemostats [111, 112]. With that said, such materials should not be left in contact with intra or extradural nerve roots due to possibility of granuloma formation [39, 53, 54, 113]. There have been reports of paraplegia from use of oxidized cellulose during thoracotomy from passage of material through the intervertebral foramen resulting in spinal

cord compression [114, 115]. Therefore, it is recommended to use only the minimum required amount and any excess material should be removed once adequate hemostasis is attained.

Biosurgical materials are increasingly applied during spinal cord surgery to help with hemostasis since opportunities for electrocautery use are limited in this setting. Bipolar cautery, although more focused than monopolar cautery, can also allow dissipation of heat from the tips inducing thermal injury to vascular and neural structures. Fibrin glues are commonly used as hemostatic agents in neurosurgical procedures, including the management of epidural, cortical, and dural sinus bleeding [116].

During surgical resection of brain tumors, from craniotomy to extradural hemostasis following dural closure, one will find that these agents are generally used throughout the procedure. For example, oxidized regenerated cellulose is widely used during ablation of lesion(s) and at the end to prevent and abate any bleeding in the remaining cavity. However, excess agent should not be left along the surgical cavity. A single layer of oxidized regenerated cellulose should be sufficient for hemostasis without significant risk. Evaluations of the efficacy and safety of polysaccharide hemospheres reported no adverse events after use in brain surgery. There have been several reports of signal anomalies on post-operative imaging mimicking residual tumor or early recurrence, or even abscess when oxidized regenerated cellulose or gelatin sponges are left in the operative field. A pediatric case series of 3 patients who underwent intracerebral surgery with use of microfibrillar collagen reported that all required second surgery for new or recurrent seizures [38]. An MRI of preoperatively suspected tumor recurrence or abscess subsequently confirmed to be microfibrillar collagen-centric necrotizing granuloma surrounded with macrophages and eosinophils. One must remain aware of the above considerations and remove any local hemostatic agent prior to dural closure.

Bleeding during surgery on the pituitary via a transsphenoidal approach may significantly impede visualization while not being conducive of the use of electrocautery [117]. The use of oxidized cellulose and Floseal (Baxter, Deerfield, IL) can be useful in this situation. Mild persistent oozing from brain tissue following excision can be controlled with application of oxidized regenerated cellulose followed by its removal from the remaining cavity prior to closure. Defects of the skull base in some cases require filling of the defect with bone graft, followed by suture and/or grafting of the dura reinforced with fibrin sealant. A minimally invasive treatment of spontaneous supratentorial intracerebral hemorrhage was also described using Floseal. Floseal was placed in 31 patients without evidence of vascular anomalies or coagulopathy following evacuation of hematoma from a 3 cm craniotomy. Hemostasis was achieved in all but 1 patient who required re-exploration [118].

A multicenter, prospective randomized study with 237 patients undergoing elective cranial surgery demonstrated PEG hydrogel (DuraSeal, Integra LifeSciences, Princeton, NJ) similarly safe when used with common dural sealing techniques (eg, sutures, autologous grafts, gelatin or collagen sponges, fibrin glues) or when used as dural closure augmentation in cranial surgery [99]. The incidences of neurosurgical complications, surgical site infections and CSF leaks were similar between treatment groups using PEG hydrogel and the control group using standard dural sealing techniques. DuralSeal was also found to be statistically significantly superior to fibrin sealant at preventing CSF leaks following posterior fossa craniotomy or craniectomy [119]. However, the special formulation of DuraSeal Exact should be used in areas where expansion can lead to neurologic compromise – such as the spinal canal [120]. This is because neurologic compromise after expansion has been described in the literature [101, 121]. This again emphasizes mindfulness to use to least amount of material to achieve closure and/or hemostasis while precluding migration or expansion of any excess materials.

8. Synthesis

Hemostasis in neurosurgery – more so that many other surgical disciplines – is challenged by the closed space environment of the brain, spinal cord, and other critical structures [3, 122, 123]. Unlike other areas in which the "bulk" or space-occupying characteristics of biosurgicals may represent a potential benefit as they expand, this is less desirable in neurosurgical applications. In the closed environment of the skull, brain, or the spinal cord – even if bone is removed to help minimize the effect of swelling from edema – a relatively small amount of compression, especially in critical areas, like the brain stem, can have devastating consequences. As discussed in previous sections of this chapter, such compressive complications, if left untreated can result in irreversible neurologic damage [94, 100–102], with resultant "Black Box" warnings clearly outlining biomaterial-specific restrictions.

Of growing concern in all aspects of surgery is the increasing utilization of anticoagulants and anti-platelet therapies – and often various combinations of both [124, 125]. While the indications for such therapies are outside of the scope of this review, it is clear that more and more patients are being prescribed agents belonging to these broad medication classes. This is of special significance in the elderly population, where anticoagulants and antiplatelet drugs are used for stroke reduction (e.g., in non-valvular atrial fibrillation); various prophylaxis indications (e.g., orthopedic surgery); and of most concern, being used without any clear indications [126]. However, many clinical factors that prompt physicians to initiate antiplatelet or anticoagulant use also increase the neurosurgical risk associated with even minor traumatic events (e.g., falls and minor head injuries). Under such circumstances, even minor neurological injuries can quickly evolve into bleeding-related catastrophes when patients are anticoagulated [127–129].

Neurosurgical interventions in the setting of traumatic (or even spontaneous) subdural, epidural, and intraventricular hemorrhage, when confounded by drugs that inherently interfere with hemostasis can compound the difficulties and risks of an already complex clinical scenario [130, 131]. The overall challenge can be magnified even further as acute reversal agents tend to be expensive, may not always be available, reliable/effective, and could result in thrombotic complications in high-risk scenarios such as multi-trauma or massive transfusion [131–134]. Furthermore, reversal algorithms and guidelines, while helpful do not always definitively address the acute problem once significant bleeding starts, and regardless of the mechanism and defect in the clotting cascade, a consumptive process may be triggered that might require a multi-faceted approach to effectively and timely manage the associated coagulopathy [134–137]. Similar to other surgical scenarios, such as major trauma and cardiothoracic surgery, at times the best way of managing bleeding is via a timely and aggressive operative intervention. The above concepts are critical in the setting of neurosurgical applications of biosurgical hemostats in that it must be recognized that "bleeding" is a complex problem and often requires a combination of tools to control. Such basic tools require an understanding of the primary question – why is this patient bleeding?

- **Mechanical bleeding** – Direct blood vessel injury that requires sutures, clips, and/or physical closure. No amount of blood products, biosurgicals, or other hemostatic agents can substitute for definitive surgical hemostasis [138].

- **Diffuse oozing** – This includes needle holes, micro-circulation (arterial and venous), that might benefit from biosurgical agents to augment the natural clotting and hemostatic process [138].

- **Defects in the clotting cascade** – either physiologic, such as inherent factor deficiencies (hemophilia), secondary to pathologic conditions (renal failure, acquired Von Willebrand's disease in aortic stenosis), or iatrogenic from medical therapies such at anti-coagulants and anti-platelet agents. Even the act of surgical incisions and minor tissue trauma can activate various components of the clotting cascade and thus complicate bleeding management [138, 139].

- **Temperature management** – Clotting is a complex enzymatic process that has evolved to be optimal at physiologic temperatures. Hypothermia, either environmental after trauma, perioperative, or therapeutic (for witnessed cardiac arrests, for example) can have potential adverse effects on hemostasis and must be considered in the context of a bleeding patient [108, 138, 139].

- Other patient factors and comorbidities can have unpredictable effects on hemostasis, but must be considered in the bleeding neurosurgical patients. Elderly, debilitated, and frail patients might be malnourished and hence have impaired protein stores which contribute to diminished clotting factor reserves – even in the setting of normal clotting tests. Patients might be taking herbal supplements (which might not even be reported in a medical record or medication lists) that have been correlated with bleeding risks [140–142].

Each of the above considerations requires a focused approach and highly specific management strategy. It is important to recognize that good surgical technique must be augmented with a broader understanding of the biologic mechanisms that contribute to the overall disease process and that there is no single tool that is ideal for all circumstances [108, 138]. Conversely, it must be recognized that there is a growing concern that using the wrong or inappropriate therapy for a given clinical scenario can be just as problematic, if not intrinsically ineffective or potentially dangerous. More so than ever in the past, optimal management of the neurosurgical patient (especially one who is bleeding) requires an in-depth and comprehensive understanding of the complex mechanisms of hemostasis pathways and the clotting cascade while also recognizing those variables, such as pharmaceutical therapies, that might adversely impact the normal balance between clotting and bleeding.

In summary, in the setting of neurosurgical bleeding management, several key concepts must be recognized:

- Use the right tool for the right job

- Sometimes more than one approach is necessary to control bleeding

- Different types of bleeding might require different management strategies

    - Difficult to access areas

    - Risk for post-operative re-bleeding

    - Compressive or expanding agents can cause devastating complications

    - Recognizing the differences between arterial and venous bleeding and how management of each might be different

- Understanding the specific reasons why bleeding is occurring and what interventions – such as biosurgical agents – should be central to the overall hemostatic management.

- Sometimes the best approach to managing bleeding is preventing it in the first place with strict attention to surgical technique and anatomy. It might sound inherently obvious, but the best way to avoid a dural sinus bleeding is to avoid injury in the first place.

9. Conclusions

Uncontrolled or difficult to control bleeding in neurosurgery is a challenging clinical problem and one that is becoming more common with wider use of anti-coagulant and anti-platelet agents in a population that is aging, becoming more frail, has more co-morbidities, and is at increasingly greater risk for neurotrauma. In addition, as more patients are undergoing major surgical interventions and re-interventions for complex neuro-axial pathologies the risks for bleeding complications also increase. Effective management of bleeding and bleeding related morbidity requires a thorough understanding of the mechanisms of bleeding and potential biologic defects in the normal hemostatic process. With such an understanding, management can be more focused and targeted towards the specific problem. Hence, an understanding of the adjuvant therapies, such as the full-spectrum of biosurgical agents that can be used to manage bleeding is imperative in achieving optimal patient outcomes.

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