Chapter

The Role of Biosurgical Agents in Dermatologic Surgery

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Abstract

Performed in an outpatient, office-based setting, dermatologic surgery reduces healthcare costs of hospitalization while maintaining low rates of surgical complications such as infection, dehiscence, and hematoma formation. However, the potential for complications requiring hospitalization or IV antibiotic therapy still exists and varies depending on patient risk factors, such as the use of antiplatelet and anticoagulant medications. Furthermore, measured outcomes in dermatologic surgery expand beyond surgical wound complications to include optimization of wound healing and reduction of scar formation, especially in cosmetically sensitive areas of the body. Biosurgical agents are increasingly being used in surgical fields to achieve hemostasis and to optimize wound healing. This chapter reviews the typical methods to achieve hemostasis in dermatologic surgery and examines the current and future role of biosurgical agents in procedural dermatology.

Keywords: biosurgical, dermatologic surgery, hemostasis, procedural dermatology

1. Introduction

Dermatologic surgery includes office-based procedures such as skin biopsies, excision, desiccation and curettage, and Mohs micrographic surgery [1]. Intraoperatively, achieving adequate hemostasis is important to clear the surgical field. Postoperatively, hemostasis is necessary to decrease the risk of dehiscence, hematoma formation, and infection, while optimizing wound healing and scar-formation. Factors that influence the choice of hemostatic agent include location, wound size, and amount of bleeding [2]. Other factors that influence hemostasis include the patient's medical history, medications, and the inherent qualities of the skin at the site of the surgery. The use of antiplatelet or anticoagulant medications may decrease the efficacy of some hemostatic agents. Concurrent medical disease such as liver cirrhosis can lead to alterations in platelets and the coagulation pathways. Elderly patients are more likely to have fragile skin as a result of chronic sun damage, and make up much of the population on antiplatelet and anticoagulation agents.

Many methods exist to achieve hemostasis intra- and post-operatively. These include topical hemostatic agents, adhesives, electrosurgery, sutures, and biologic agents. This chapter provides an overview of the methods to achieve hemostasis and of the use of biosurgical agents in dermatologic surgery.

2. Physiologic hemostasis

An understanding of physiologic hemostasis is necessary to determine what hemostatic agent is most appropriate. Physiologic hemostasis occurs via three stages: initiation, amplification and propagation [1]. The initiation phase involves endothelial injury leading to exposure of tissue factor (TF) [1]. The exposed TF binds and activates Factor VII, and the resultant complex activates Factors X and IX, ultimately leading to formation of Factor II (thrombin) [1]. This mechanism of endothelial injury leading to coagulation is also known as the intrinsic pathway to achieve hemostasis [1].

Simultaneously, exposure of endothelial collagen begins the amplification stage. Circulating von Willebrand factor (vWF) binds to exposed collagen on one end and attracts platelets at the other end. Meanwhile, the thrombin that was created in the initiation phase will activate these platelets, stimulating release of clotting factors and for increased production of thrombin [1].

In the final, propagation phase, thrombin converts fibrinogen to fibrin into a network that stabilizes the platelet clot in a manner that is calcium dependent [1]. Thus, the induction of endothelial injury results in hemostasis via the interaction of multiple coagulation factors creating a platelet clot.

Impairments in hemostasis may be genetic or inherent to the patient and can involve any step of the pathway described above. One example of a bleeding diathesis is the genetic lack of coagulation Factor VIII leading to hemophilia A [1]. These patients have a prolonged bleeding time and can have large hematomas as a result of minor injuries. When patients are on antiplatelet and anticoagulant medications such as aspirin or warfarin, respectively, the duration of bleeding is prolonged because of a therapeutic and desired reduction in clot formation. Although these medications are continued for routine dermatologic surgery, such factors must be taken into account when determining appropriate methods of hemostasis.

3. Methods to achieve hemostasis

3.1 Mechanical agents

One of the simplest methods to achieve hemostasis is mechanical compression [1]. Application of pressure to the capillaries results in platelet aggregation and thrombus formation [2]. Mechanical compression is routinely used in the dermatology clinic for superficial wounds such as following a biopsy procedure. It is less useful in the intraoperative setting to acutely reduce bleeding. Temperature regulation can also induce hemostasis. The vasoconstriction caused by decreasing the temperature of the tissue will decrease the rate of bleeding. However, there is a risk of tissue damage and rebound vasodilation [2].

3.2 Physiologic agents

Physiologic agents utilize the body's inherent mechanisms to control the rate of bleeding. Epinephrine, frequently mixed with local anesthetics for use in dermatologic procedures, induces vasoconstriction [2]. The rare side effect of tachyarrhythmia is usually seen with systemic use [2] and can be safely avoided by local injection. One side effect that may be seen in dermatologic procedures is postoperative bleeding following rebound vasodilation once the effects of epinephrine have worn off [2]. Cocaine is another vasoconstrictor that may decrease

bleeding, but it is rarely used dermatology due to its side effect profile and high potential for illicit use [2].

When applied to wounds, tranexamic acid causes competitive inhibition of the activation of plasminogen [2]. This results in decreased levels of plasmin, which functions to break down fibrin clots. Therefore, tranexamic acid decreases bleeding by reducing the breakdown of clots. It is easy to apply topically in the setting of dermatologic procedures [2]. Hydrogen peroxide is easily available and has mild hemostatic properties by enhancing platelet aggregation [2]. It has antimicrobial properties and plays a role in wound care [2]. One downside to its use is inhibition of wound healing [2].

3.3 Biologic agents

Biologic agents influence the coagulation cascade to enhance clot formation. Most involve thrombin and fibrin [2], two important steps in the coagulation cascade. As described in the "Hemostasis" section, the coagulation cascade results in the formation of thrombin. Thrombin is essential to convert inactive fibrinogen to fibrin, which forms a mesh-like network with platelets and creates a stable platelet plug at the site of endothelial injury. This platelet plug is resistant to degradation until purposely broken down by plasmin. In biologic agents used for hemostasis, the concentration of thrombin determines the speed of clot formation and tensile strength [2]. The concentration of fibrinogen determines the mechanical strength [2]. There are four major types of biologic agents: thrombin, fibrin sealants, hemostatic matrix, and platelet gels and sealants [2].

Thrombin can be applied by itself and is available in a variety of forms including spray, liquid, hypodermic injection, or saturation of gauze or sponge [2]. It is useful in patients who are on antiplatelets and anticoagulants [2] because it provides the necessary thrombin to locally activate fibrinogen to fibrin at the site of the surgical wound. It can also be left within the surgical wound as the resulting fibrin clot will be reabsorbed over time [2]. Although there are recombinant forms, many thrombin agents are bovine- or human-derived and therefore have antigenic potential i.e. an associated risk of antibody formation [2]. It can also induce diffuse intravascular coagulation (DIC) if it is given in large enough quantities to cause systemic absorption or if it is erroneously injected into the circulatory system [2]. Cost may be a limiting factor [2].

Hemostatic matrix combines thrombin and gelatin but must be removed from the wound following hemostasis [2]. Thrombin and hemostatic matrix rely on fibrinogen present in blood [2]. They are not useful in patients with afibrinogenemia as they activate the patient's circulating fibrinogen [2]. Hemostatic matrix can become difficult to use after three minutes following preparation [2]. Fibrin sealants contain both thrombin and fibrinogen but require preparation of the wound bed as they are denatured by antiseptics [2]. Fibrin sealants also require stirring and heating prior to application [2]. Platelet gels and sealants contain bovine collagen and thrombin and can be used in reconstructive surgery [2]. They require operator skill for preparation and have a high cost and antigenic potential [2]. These products are unique in that they act as hemostatic agents, create a waterproof barrier and function as a tissue adhesive [2]. However, use of fibrin sealants for routine dermatologic surgery is cost-prohibitive [1].

3.4 Chemical agents

Chemical agents are caustic substances that create a localized destruction of tissue to cause thrombus formation and include zinc paste, Monsel's solution, silver

nitrate and aluminum chloride [2]. Zinc paste is rarely used in dermatology as it causes irritation and pain and cannot be used in wounds that will ultimately be closed [2]. Monsel's solution is an acidic solution that oxidizes when exposed to air [2]. There is an increased risk of dermal fibrosis and inflammation, along with dyspigmentation from the deposition of iron particles into the dermis that may confuse the clinical picture if considering re-excision [2]. Silver nitrate presents a similar but much rarer risk of tattoo formation due to the deposition of silver particles [2]. The precipitant obstructs blood vessels and leads to eschar formation [2]. However, the formation of eschar may result in tissue damage and impaired wound healing, and patients typically experience stinging on application [2]. Aluminum chloride leads to the hydrolysis of hydrogen chloride and leads to coagulation via constriction of blood vessels and activation of the extrinsic pathway [2]. Its cost is affordable, and it is commonly used in dermatology for small wounds left to heal by secondary intention [2]. Monsel's solution, silver nitrate and aluminum chloride are also easy to store [2].

3.5 Physical agents

All physical agents have absorptive properties that remove fluid while leaving behind concentrated coagulants [2]. When applied to the wound, they create a three-dimensional meshwork where platelets aggregate and form a clot [2]. The physical agent absorbs blood during this process. These are practical and cost-effective for dermatologic surgery [1]. They include gelatin, cellulose, microfibrillar collagen, and hydrophilic polymers.

When applied to the wound, gelatin increases to twice its size but can also cause compression of nearby structures if the site is closed [2]. Wounds left to heal by secondary intention are not confined and gelatin can be applied for hemostasis without the risk of compression [2]. Gelatin is available in a variety of forms with brand names such as "Gelfoam", "Gelfilm" and "Surgifoam" [2]. It is relatively affordable, nonantigenic in tissue, and can be left inside the wound during closure [2]. It is useful in the setting of small vessel bleeding commonly encountered in dermatologic procedures [2].

Cellulose is able to absorb up to seven times its weight [2]. It is available in mesh, fiber, and powder form [1]. It is applied to the wound and is ultimately broken-down during healing [1], but its slow absorption increases the risk for foreign body reactions [2].

Microfibrillar collagen causes binding of clotting factors to the physical matrix and is available in a powder, sheets, and fleece forms [2]. However, it is dependent on platelet activation and is less effective if patients are thrombocytopenic [2]. It is effective in patients on heparin therapy and is normally used on large surface areas [2]. In contrast, hydrophilic polymers do not rely on the clotting cascade and are useful in patients on anticoagulants [2]. Hydrophilic polymers are not metabolized by the body and can only be used in wounds left open to heal by secondary intention, or they may be used temporarily for hemostasis before final wound closure [2].

3.6 Synthetic, mechanical adhesives

Cyanoacrylates are synthetic acrylates that rapidly polymerize to form a water-resistant barrier [2]. These can be applied to low-tension cutaneous wounds and misapplication can be easily corrected with the application of acetone [2] Other synthetic mechanical adhesives such as polyethylene glycol hydrogels and glutaraldehyde cross-linked albumin are primarily used in cardiac surgery [2].

3.7 Hemostatic dressings

Chitin is present naturally in arthropod skeletons [2]. When applied to wounds, it causes vasoconstriction, seals the wound, and can be removed with saline if applied incorrectly [2]. Of note, these products should be avoided in patients with allergy to shellfish [2]. Mineral zeolite is an inexpensive and stable dressing that contains inert minerals and absorbs liquid via an exothermic process to increase the concentration of coagulation factors [2]. Chitin and mineral zeolite are easily stored [2]. Dry fibrin dressing is freeze-dried thrombin and fibrinogen contained on gauze [2]. It can be rapidly applied to wounds but has a high cost [2].

3.8 Electrosurgery

Electrosurgery is the use of alternating high frequency current to obtain hemostasis [3]. The effect on tissue depends on the type of device, waveform, and type of electrode [3]. An understanding of terminology is important for appropriate use. Monoterminal refers to the use of low power current that disperses to the environment and does not require grounding [3]. Biterminal passes current through the tip and patient, into a grounded electrode and back to the power source [3]. Monopolar allows both coagulation and cutting modes through a single electrode. Bipolar delivers energy current via two electrodes [3]; the two electrodes in the bipolar cautery are located close together and result in decreased depth of tissue injury [3]. Electrocautery refers to thermal energy causing hemostasis [3]. This method is usually used in patients with implanted cardiac defibrillators (IDC) due to no current delivered to the patient [3]. Of note, there is a risk of direct thermal injury to the ICD if electrocautery is performed at the site of implantation [3]. Electrodessication, also known as hyfrecation, utilizes a monoterminal, high frequency, low amperage current to induce slow heating of tissue close to the tip, causing fluid loss of local and superficial "mummification" [3]. In electrofulguration, the electrode delivers high frequency, low amperage current through a monoterminal circuit [3]. The ionization of the surrounding air creates a localized "spark" without directly contacting the tissue and causes localized coagulation and barrier formation [3]. Electrocoagulation (Bovie) uses a biterminal circuit to cause cutting, coagulation, or a mix of both, while electrosection uses a biterminal circuit to cut and vaporize tissue with little damage to adjacent tissue. Electrosection is rarely used in dermatologic surgery [3].

3.9 Sutures

Sutures play an important role in hemostasis. The type of suture and placement is determined by the size of the wound, the location on the body, and type of repair performed. While most absorbable sutures are synthetically derived, surgical gut suture is created from collagen derived from sheep or cow intestines [4]. Surgical gut suture are multifilament sutures subdivided into plain, fast absorbing, and chromic [4]. They have low tensile strength ranging from 3–7 days for fast absorbing, 7–10 for plain, and 10–21 days for chromic gut sutures [4]. Time to complete absorption may be variable, and tissue reactivity and allergy are disadvantages to their use [4].

Surgical silk is the only naturally derived, nonabsorbable suture material [4]. It is created from protein fibers harvested from the cocoon of silkworm larva [4]. Its excellent knot strength and ease of handling must be weighed against low tensile strength and high potential for tissue reactivity [4]. Although it is classified as nonabsorbable, it is slowly absorbed over the course of two years [4].

4. Biosurgical agents in wound care

While dermatologic surgery involves outpatient procedures with minimal blood loss, appropriate wound care is necessary for optimized healing. Benign lesions such as cysts and lipomas typically heal with minimal scarring after removal [1]. Skin cancer excisions and Mohs Micrographic surgery can result in large and irregularly shaped defects where complete re-approximation is not always achievable [5]. The resulting closures can be fragile and in cosmetically sensitive areas [5]. Wound care of linear closures as well as larger defects is an essential component of successful dermatologic surgery outcomes.

There are two types of healing: primary intention and secondary intention [6]. Healing by primary intention occurs after a direct side-to-side closure of an incision [6]. Healing by secondary intention occurs when a defect is left to heal on its own without closure [6]. Defects that heal by primary intention result in minimal scarring [6]. Flaps and grafts attempt to force primary intention healing and thereby minimize scarring [6]. Defects that are left to heal by second intention are left "open" while the healing process takes place [6].

The surgical site defect can take one of two courses. Acute wounds have no underlying healing pathology and heal in a predictable and timely fashion [4, 6]. Ideally, all cutaneous surgery lesions heal as acute wounds. Chronic wounds typically involve underlying pathologic impairment of wound healing [4, 6]. Chronic wounds can occur when there are impairments in wound healing and medical comorbidities, such as in the elderly population [4, 6]. The implementation of biosurgical materials to promote healing depends on the type of wound.

4.1 Dressings

Basic modern wound care consists of wound debridement, packing, topical therapy, and dressings. Various forms of biosurgical materials are available in wound care and are primarily implemented for chronic or recalcitrant wounds [1]. Often derived from biomaterials, dressings physically protect the wound from trauma and bacteria, compress the wound to encourage hemostasis, minimize fluid and heat loss, and absorb drainage [7]. Acute wounds heal best when they are moist, but it is important to minimize maceration or excessive moisture that can cause tissue break down [8, 9].

Wound dressings are further broken down as nonadherent, absorptive, and occlusive. Nonadherent fabrics can be either hydrophobic, which provide better occlusion but worse drainage, or hydrophilic, which provide better drainage but worse occlusion [10]. Alginates are a popular biologically derived material used for dressings. This cellulose like material is made from seaweed and calcium salts, which react with the wound to form a hydrophilic gel [10]. It is a hemostatic, highly absorbent, and non-adhesive dressing. It is typically used in deeper wounds [10]. Newer materials used as occlusive dressings include collagen and hyaluronic acid. Collagen dressings are derived from type I bovine collagen and provide a matrix to promote wound healing [10]. They are used primarily for moderately exudative and recalcitrant wounds. Hyaluronic acid is an absorbent polymer, also found in the skin. As a dressing, it forms a biodegradable hydrophilic gel. It facilitates granulation tissue formation and epithelialization [10].

There is a wide array of commercially available dressings (roughly 3000) that include these materials in adhesive, gel, and powder forms [11, 12]. These dressings are stored at room temperature with a minimum shelf life of three months, and thus, can be implemented with relative ease in an outpatient setting [12].

4.2 Grafts

Flaps and grafts promote wound healing by primary intention by creating a linear closure. They can be considered a type of dressing. A graft is skin separated from its blood supply and transferred to a new location [13]. They may be some combination of the following: autografts or skin grafts derived from the patient, allografts derived from the same species, and xenografts derived from a different species. Full thickness grafts contain the epidermis, dermis, and subcutaneous tissue. Split thickness grafts consist of just the epidermis and part of the dermis. Composite grafts consist of skin as well as cartilage [10].

Grafts can be further delineated as either biologic or biosynthetic. Biologic full thickness grafts are usually allografts frequently utilized during Mohs micrographic surgery [5]. They are usually derived from the pre- or postauricular area, the inner arms, nasolabial folds, or clavicular area [13]. Full thickness grafts are best for cosmetically sensitive areas but have a higher risk of failure due to a greater blood supply demand [13]. Split thickness grafts can be used for skin cancer removals in less cosmetically sensitive areas, such as the lower leg, or in areas with a high risk of recurrence [13]. They are usually derived from the donor thigh or buttock [13].

Skin substitutes or biosynthetic grafts are derived from biological materials (**Table 1**) [10]. They are epidermal, dermal, or composite (derived from more than one species) [10]. Epidermal grafts include cultured epidermal autograft or allograft. Cultured epidermal autografts are epidermal sheets grown from the patient and are used for large excisions, chronic ulcers, or severe burns [10]. They can cover a large area and often yield good results but take a few weeks to grow and are both delicate and expensive [10]. Cultured epidermal allografts are usually derived from neonatal foreskin [10]. This skin releases its own growth factors and is progressively replaced by the patient skin [10]. These are immediately available and help avoid a donor site wound; however, they are expensive and carry a risk

Type	Biological Material
Epidermal	
Cultured autografts	Epidermal sheets of keratinocytes grown from the patient
Cultured allografts (Epicel)	Neonatal foreskin
Dermal	
Cryopreserved allografts	Cadaver skin
Chemically treated cryopreserved allograft (Alloderm)	Cadaver skin with decellularization, matrix stabilization, and freeze drying
Porcine derived chemically treated collagen	Type I porcine collagen
Bovine collagen chondroitin sulfate over silastic (Integra)	Type I bovine collagen and chondroitin 6-sulfate
Fibroblasts in bioabsorbable mesh (Dermagraft)	Human neonatal foreskin fibroblasts
Composite	
Human keratinocytes layered on bovine collagen (Apligraft)	Human keratinocytes and fibroblasts bovine type I collagen

JAMA 2000.

Table 1.
Skin substitute grafts. Adapted from Bello YM, Phillips TJ. Recent advances in wound healing.

for disease transmission [10]. Cultured epidermal allografts can be used for either acute or chronic wounds [10].

There are also a variety of dermal skin substitutes. Cryopreserved allografts are derived from cadaver skin and are typically reserved for burns [10]. They are immediately available, but they must be kept frozen with a shelf life of up to five years [12] and also carry a risk for disease transmission [10]. Chemically treated cryopreserved grafts are cadaver grafts that have been treated to remove antigens [10]. They therefore carry less risk for rejection but require viral screening [10].

Porcine xenografts are less expensive than their counterparts (refer to **Table 1**) and can be used as temporary dressing or to help re-epithelialize surgical sites [14]. Porcine xenografts and cryopreserved allografts have been shown to be equally effective clinically [15]. Xenografts have a long shelf-life, may be stored at room temperature, and can be rapidly applied to wounds and can be sutured or held in place with a dressing [14]. Porcine grafts can also be replaced or removed, permanently grafted, or left to desiccate and fall off as wounds heal [14].

Porcine derived chemically treated collagen is a dermal xenograft skin substitute [16]. They are useful because they have a long shelf life, carry no human disease, and are immediately available. However, they lack extensive evidence of their efficacy [10]. Bovine collagen chondroitin sulfate over silastic is another dermal xenograft skin substitute. It works similarly to porcine derived collagen and has a shelf life of two years; it is easier to handle than the more fragile grafts but is susceptible to infection [10]. Fibroblasts in bioabsorbable mesh are allogeneic human neonatal foreskin fibroblasts on nylon bioabsorbable mesh. They are advantageous because they are immediately available and result in less wound contracture, but they are expensive and must be stored in cold temperatures [10].

Composite skin substitutes include human keratinocytes layered on bovine collagen. These do not have the normal skin appendages including nerves and vessels, and thus are immunologically inert. They are useful since they are immediately available and also easy to handle but only have a shelf life of ten days and are very expensive [10].

5. Conclusions

While Dermatologic surgery involves outpatient procedures, adequate hemostasis is important intra- and postoperatively and appropriate wound care is necessary for optimized healing. The use of adjunctive materials including biosurgicals to promote hemostasis and healing depends on the type of wound, type of bleeding, amount of bleeding, and patient factors. Properties of the adjunctive agent affect the decision as well, such as speed of hemostasis, ease of application, and tissue reactivity.

Conflict of interest

The authors declare no conflict of interest.

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