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# Topical hemostatic agents in surgery: review and prospects.

## *Agentes hemostáticos tópicos em cirurgia: revisão e perspectivas.*

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A B S T R A C T

Hemostasis plays a critical and fundamental role in all surgical procedures. Its management has several key points that start with good operative technique and adequate anesthetic support. Certain situations, such as severe bleeding resulting from penetrating trauma, do not depend exclusively on the control of the surgical team and require the support of new solutions that decrease or control bleeding. Since ancient times, a hallmark of medicine has been to act in the control of hemorrhage, and more recently, in the facilitation of hemostasis by the application of topical agents by either manual compression or modern agents. In the last decade, the number of different topical hemostatic agents has grown dramatically. For the modern surgeon to choose the right agent at the right time, it is essential that he/she understands the mechanisms of action, the effectiveness and the possible adverse effects related to each agent. Thus, the great variety of topical hemostatics, coupled with the absence of a review article in the national literature on this topic, stimulated us to elaborate this manuscript. Here we report a detailed review of the topical hemostatic agents most commonly used in surgical specialties.

**Keywords:** Hemostatic. General Surgery. Hemostasis. Surgical. Hemostatic Techniques. Surgical Procedures. Operative.

## INTRODUCTION

Hemostasis plays a critical and fundamental role in all surgical procedures. Its management has several key points that start with good operative technique and adequate anesthetic support. Certain situations, such as severe bleeding resulting from penetrating trauma, do not depend exclusively on the control of the surgical team and require the support of new solutions that decrease or control bleeding.

The use of topical hemostatics is an old concept, used in different ways by ancient civilizations. The Egyptian people made use of a mixture of wax, grease, and barley in an effort to stop bleeding. In ancient Greece, priests and healers of the time applied hemostatic herbs to war wounds[1]. Recently, advances in biotechnology have resulted in the development of topical hemostatic agents that are currently available to the surgeon. Such agents range from absorbable topical hemostats, such as gelatins, micro fibrillar collagen and regenerated oxidized cellulose, to biologically active topical hemostats such as thrombin, biological adhesives, and other combined agents.

The wide variety of topical hemostatics added to the low frequency of review articles in the national literature on this topic stimulated us to elaborate this manuscript. We carried out a review in the electronic databases PUBMED, EMBASE, MEDLINE and LILACS, searching for manuscripts in English, Portuguese, French and Spanish. We will presented the topical hemostatic agents most commonly used in surgery, dividing them into absorbable, biological and synthetic, as listed in table 1.

## ABSORBABLE AGENTS

### Regenerated oxidized cellulose (Surgicel Original®, Surgicel Nu-Knit®, Surgicel Fibrillar®, Interceed®, Gelitacel®)

Simple oxidized cellulose was first proposed in 1942 in the United States. In 1960, a new topical hemostatic - regenerated oxidized

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***Table 1.*** *Types, trade name and mechanism of action of topical hemostatic agents.*

| Topical hemostatic | Commercial name | Mechanism of action |
|---|---|---|
| Oxidized regenerated cellulose | Surgicel Original®, Surgicel Nu-Knit®, Surgicel Fibrillar®, Interceed®, Gelitacel® | Physical matrix for initiation of the clot. The low pH promotes antimicrobial effect |
| Gelatins | Surgifoam®, Gelfoam®, Gelfilm®, Gelita-spon®, Geli putty® | Physical matrix for initiation of the clot |
| Gelatine + Thrombin | Floseal®, Surgiflo® | Combination of effects of gelatin and thrombin |
| Microfibrilar collagen | Instat®, Helitene®, Helistat®, Avitene®, Avitene flour®, Avitene Ultrafoam®, EndoAvitene®, Avitene Ultrawrap® | Platelet Adhesion and Activation |
| Fibrin sealants | Evicel®, Tisseal®, Crosseal®, Quixil® | Thrombin and Fibrinogen are combined at the time of application. Thrombin degrade Fibrinogen into fibrin, forming clot |
| Topical thrombin | Evithrom®, Recothrom®, Thrombin-JMI® | Converts Fibrinogen into fibrin to form clot. Promotes activation of coagulation factors |
| Glutaraldehyde and bovine albumin adhesive | BioGlue® | Glutaraldehyde interacts with bovine albumin and protein cell at wound site to form a resistant matrix |
| Cyanoacrylate adhesives | Dermabond®, Omnex® | Liquid monomers form polymers in the presence of water and glue two surfaces |
| Polyethylene glycol | CoSeal® | Two polyethylene glycol polymers mix and react at wound site |

cellulose (ROC) - appeared on the market with the launch of Surgicel®, the only one hitherto not derived from human or animal elements[2]. ROC is therefore a topical hemostatic of vegetal origin, manufactured by the regeneration of pure cellulose in interwoven (cotton) fabric that is subsequently oxidized. Its functional unit is anhydroglucuronic acid. The regenerated oxidized cellulose is easy to apply and manipulate in surgery because of its loose interwoven fabric, resembling a cotton swab (Surgicel Fibrillar®, Gelitacel®) or a small piece of mesh (Surgicel Nu-Knit®), thus acting as a support matrix for the initiation and formation of the clot. The regenerated oxidized cellulose is not sticky, adheres to surgical material, can be molded in different shapes and sizes, does not chip in the presence of liquids and supports compression without losing its property. This material should not be infused into aqueous media prior to use, since it has improved hemostatic activity when applied dry.

Both commercial forms of ROC lower the local pH once applied. The acidic pH causes hemolysis, which explains the brownish color of the material when in contact with blood. Hemoglobin resulting from hemolysis reacts with local pH (acid) to form acid hematin. One of the theoretical advantages of low pH is the potential antimicrobial action and caustic action, potentiating hemostasis and the formation of an artificial clot[1]. The low local pH, however, has the disadvantage of inactivating the action of biologically active coagulants, such as thrombin, thus preventing the use of ROC in conjunction with other biological hemostatic agents. In addition, the acidic nature of ROC can increase the local inflammatory process and delay the normal healing process[3]. Another important point, which may induce the surgical team to submit their patient to unnecessary intervention, and which can also be attributed to gelatinous-based hemostats, is the postoperative appearance of an image with a hyperdense halo and hypodense center at tomography, which may be confused with an abscess. Non-common images that generated diagnostic doubt were recently reported in the literature in both adults and pediatric patients. More than that, surgical complications were reported with the use of ROC in cases of severe bleeding[4,5]. The dissolution of ROC can range from two weeks to a few years, depending on the amount of the product used[3].

**Gelatins (Surgifoam®, Gelfoam®, Gelfilm®, Gelita-spon®, Geli putty®, FloSeal®)**

Gelatin is a hemostatic agent made from hydrolyzed and purified animal collagen (swine, sheep or equine dermis or tendon). It was introduced in the market in 1945 and few advances in its form and composition have been made since[6]. Although its mechanism of action is not fully known, it is believed to act more physically than chemically in the coagulation cascade[7]. Thus, as in the ROC case, gelatins are useful as a physical matrix for clot initiation.

The gelatin matrix can be used in different forms: sponges, powder and sterile physiological solution to form a foamy appearance when mixed or saturated in purified thrombin. The foamed solution is associated with a decrease in infection at the site of application and has been shown to be useful in reducing bleeding of bone origin, as in sternotomies and neurosurgeries.

An important property of the different forms of gelatin is its ability to absorb more than 40 times its weight in blood and fluids and its ability to expand its volume by 200% *in vivo*. This means that gelatin forms increase their volume more than the topical hemostatics based on collagen and regenerated oxidized cellulose. Although this property provides good hemostatic mechanical action, it can also be seen in some ways as a negative feature in some specialties, especially when used in confined spaces or near nerve structures, generating complications of compressive origin. The general and trauma surgeon can benefit from this property in penetrating traumas. Transfixant wounds from solid organs, in particular, may be handled with this material alone or in conjunction with ROC.

Studies reporting complications related to the use of gelatins, such as formation of abscesses or granulomas, are rare. Some attribute these complications to doubtful postoperative radiological images, later identified as topical gelatine hemostatics[8,9].

The gelatin matrix is absorbed within four to six weeks and is referred to as non-antigenic, although it is derived from products of animal origin. Unlike regenerated oxidized cellulose, the pH of the gelatin matrix is neutral and therefore can be used

in conjunction with thrombin or other hemostatic agents to enhance hemostatic action. Affordability, ease of use, low price and good hemostatic activity make topical hemostats with gelatin matrix a popular tool for reducing the morbidity caused by hemorrhage.

A major breakthrough in gelatin matrix hemostats came with the development of a product called FloSeal®, approved for commercial use, in 1999, in the U.S., deserving to be set apart in this section. Unlike the other topical hemostats with gelatin matrix, FloSeal® is a gelatin matrix based on bovine collagen containing microgranules, crosslinked with glutaraldehyde (biological glue) and human thrombin solution that are mixed at the time of use[10,11]. In contact with blood, the gelatin particles swell and induce a buffering effect. This feature allows it to be more effective in controlling moderate bleeding compared with other agents. FloSeal® has been be superior to Gelfoam-thrombin in cardiac surgeries and has reduced bleeding when used in open nephrectomies and laparoscopy[12]. Although not important in certain surgical interventions, FloSeal's liquid property facilitates application in certain procedures and techniques, especially in minimally invasive surgery. It has been demonstrated that the use of FloSeal® in surgery is safe and effective[10,12].

**Microfibrillary Collagen (Instat®, Helitene®, Helistat®, Avitene®, Avitene flour®, Avitene Ultrafoam®, EndoAvitene®, Avitene Ultrawrap®)**

Developed and marketed in the 1970s, topical microfibrillar collagen (TMC) hemostats are produced by purifying bovine, equine or goat collagen fibers (dried protein), processed into microcrystals and then handled in commercial forms. The Avitene® brand was first launched in powder form, and is still commonly used. All types of collagen-based hemostats gained widespread early use when they appeared to be more effective than topical gelatin-based hemostatics. Collagen-based products activate the intrinsic pathway of the coagulation cascade, while the gelatine-based hemostats induce hemostasis through physical properties. In some randomized clinical trials, microfibrillar collagen hemostats were superior to regenerated oxidized cellulose, demonstrating a statistically significant reduction in blood loss[13]. Advances in the field of collagen-based hemostats have been the launch of new commercial formats. The first collagen-based topical hemostatic (Avitene®) was initially available in powder form, and today the product line has expanded into tissue-like materials, as well as sponge-shaped and small pads or plaques (Instat®).

TMC provides a generous surface area that, when in contact with blood, allows adhesion and platelet activation, promoting thrombus formation within two to five minutes[14]. Considering that its mechanism of action depends on platelet activation, TMC is less effective in patients with severe thrombocytopenia or coagulopathies. However, it successfully reaches hemostasis even in heparinized patients. Unlike gelatins, TMC does not increase in volume, and is absorbed in less than eight weeks. It should be applied to bleeding surfaces with a dry instrument and not with the surgeon's hands, as it tends to adhere to the gloves. Microfibrillar, collagen-based hemostats have been used successfully to control areas of extensive bleeding. In laparoscopic procedures, options available on the market (Endo-Avitene®), which are characterized by the shape of laminated sheets, are available with an applicator that facilitates the introduction through trocars. As with regenerated oxidized cellulose, it is recommended to remove the excess TMC from the surgical site after adequate hemostasis, as it

may bind to neural structures and cause pain or numbness. Topical site infections were described as more frequent with TMC-based hemostatics when compared with ROC-based ones. Complications and doubts in imaging studies related to procedures in Neurosurgery were widely reported, leading researchers to perform animal safety and efficacy studies, specifically in this surgical area[15].

## BIOLOGICAL AGENTS

### Fibrin sealants (Evicel®, Tisseal®, Crosseal®, Quixil®)

The Fibrin sealant was first mentioned in the literature in 1909, in Europe. Studies resumed in the 1940s after the availability of purified thrombin and its use became common in different surgical specialties, including during the First World War. In the USA, it was approved for use in humans only in the 1980s (Tisseal®), after proving to be safe and effective[16].

The classic fibrin sealant consists of clustered human lyophilized fibrinogen and bovine or human thrombin, sometimes also containing concentrated coagulation factor XIII and aprotinin[17]. Factor XIII is a proenzyme activated by thrombin in the presence of calcium ions (fibrin stabilizing factor). Once activated, factor XIII forms cross-links between fibrin chains, stabilizing the clot formation. Being the oldest type of glue on the market, several products are available, with varying concentrations of its ingredients. This modifies the coagulation properties. Blood clots' resistance to traction is a function of several factors and the concentration of fibrinogen is of great importance. Thrombin has a major impact on the speed and integrity of coagulation and, indirectly, on clot stability[18]. Aprotinin is a protease inhibitor (bovine lung tissue) that inhibits trypsinin, plasmin and kallikreins, delaying plasmin-mediated clot lysis. Fibrin glues are applied through a double syringe technique. Ideal application requires a dry operating field. Fibrin glues are particularly effective when applied prior to bleeding. In this situation, fibrinogen may polymerize before blood pressure increases the flow of the local microcirculation. When used after the onset of bleeding, one should apply local pressure over the wound to allow polymerization[19].

The combination with cellulose, gelatin and/or collagen (wool, mantas or other matrices) with procoagulant substances, either fibrin or thrombin, is a newly created approach (Surgiflo®: gelatin + thrombin) to increase the effectiveness of topical hemostatics, being classified as solid matrix fibrin sealant. These products combine the mechanical effects of a time buffer with the hemostatic effects of the fibrin sealant. The collagen matrix induces platelet aggregation and stimulates factor XII coagulation. Upon contact with liquid, the solid components dissolve and form a viscous fibrin clot between the matrix and the wound's raw surface. A compression period is required for polymerization of the sealant components.

Fibrin topical hemostats that do not require compression can be obtained with the aid of liquid-absorbing particles that increase in size, dissolve in liquid matrix, and adhere to surgical wounds (FloSeal®). They are classified as liquid matrix fibrin sealants. This material does not require a dry surgical field for application. Other products (CoStasis®, Vitagel®) approved for use in humans in 2000 in the USA are composed of a microfibrillar collagen compound and bovine thrombin, mixed in a syringe with plasma (autologous - containing fibrin and platelets) from the patient removed and centrifuged during surgery[1]. Plasma components provide fibrinogen, which is cleaved by thrombin to

form a gelatinous matrix of collagen-fibrin. Like the other local hemostats combined, it is an expensive product, and its success depends on the surgeon's experience[1,20].

In 2003, the American Red Cross introduced Crosseal®. It is composed only of products of human origin (fibrinogen and clustered plasma thrombin as well as tranexamic acid)[21]. In 2004, Schwartz *et al*.[22] reported, in a multicenter prospective randomized study, Crosseal®/Quixil® as the most effective hemostatic, with less time for effective hemostasis, less intraoperative bleeding and less induction of complications when compared with the control group (Avitene®, Surgicel®, Surgicel NuKnit®, Gelfoam, Gelfoam + thrombin).

Another agent that recently reached the market is Evicel®, which does not contain fibrinolytic inhibitors and requires a minimum pre-application preparation time, making it easier to use. It can be used in the form of spray, presenting satisfactory hemostasis in bloody surfaces such as those resulting from hepatic trauma. In our experience, Tisseel®, Quixil® and Evicel® fibrin glues are especially suitable for controlling low pressure (venous) bleeding and from bloody surfaces such as kidneys, liver and spleen.

Initially, the clinical applications for fibrin sealants were largely limited to Cardiac, Vascular, Oral, Maxillofacial and Reconstructive Plastic Surgery, but recently several applications are being discussed in the literature for other Specialties such as Trauma Surgery, Urology, Obstetrics and Neurosurgery. Specifically in Trauma Surgery, some authors have demonstrated that the use of fibrin sealants in severe hepatic trauma excluded the need for packing of the organ[23,24].

Although fibrin sealant was one of the first hemostatic agents used in clinical practice, the slow development of the technology, the initial obstacles to FDA approval in the USA and its limited subsequent availability led to a relative paucity of prospective clinical research with fibrin sealants. Being a material with great use potential and relatively poorly studied, fibrin sealants had an interesting space for new researches in surgery. A new commercial form of fibrin sealant that has recently been approved for use in humans by the FDA, following several studies in experimental models, was TachoSil®[25-27], which resembles a spongy plaque and demonstrated its utility not only as a hemostatic, but also in intestinal anastomoses and in tracheobronchial fistulas due to its high adhesive capacity[25,28]. To date, no adverse effects have been related to the use of TachoSil®, although there have been reports in the literature of the presence of antibodies after its application, but without clinical expression[27].

**Topical thrombin (Evithrom®, Recothrom®, Thrombin-JMI®)**

Thrombin is a natural enzyme with roles in hemostasis, inflammation and cell signaling. It is formed from prothrombin, as a result of the activation of intrinsic and extrinsic coagulation pathways, and forms the base of the fibrin clot, promoting the conversion of fibrinogen to fibrin. Thrombin has been purified from several sources and used as an adjunct to topical hemostasis for more than 60 years. Until recently, the only commercially available thrombin was derived from bovine plasma (Thrombin-JMI). Although it been an effective tool to stop bleeding, bovine thrombin has been shown to induce an important immune response[29]. Several studies have documented a number of clinical events that accompany human exposure to bovine thrombin, and include the development of antibodies against thrombin, prothrombin, factor V, and cardiolipin[29]. Patients on hemodialysis with high levels of antibodies against topical bovine thrombin

had an increased incidence of vascular access thrombosis, severe coagulopathy and bleeding after exposure to bovine thrombin[30].

Because of these concerns, researchers have developed thrombin derived from human plasma and recombinant human thrombin. In 2007, Browman *et al*.[31] demonstrated, in a comparative study between recombinant human thrombin and bovine thrombin, that human recombinant thrombin demonstrated the same efficacy in surgical hemostasis, a similar safety profile, and a significantly lower immune response than bovine thrombin.

## SYNTHETIC AGENTS

### Glutaraldehyde and bovine albumin adhesive (BioGlue®)

The glutaraldehyde and bovine albumin adhesive (GBAA) consists of a solution of 10% glutaraldehyde and 45% bovine albumin solution purified by precipitation, heat and chromatography radiation[32]. It was approved for use in the USA in 1999, being commercially presented in a syringe with two separate compartments and the same dispensing nozzle, when its components are then mixed at the time of application. Within 20 seconds the adhesive has 65% binding power and obtains its full binding strength in two minutes, regardless of the temperature or the application medium (air or water)[33]. In a study in which BioGlue® was used as a hemostatic agent in 79 cardiac surgeries, there was success in 78 cases.

Although some research in cardiac surgery suggests the use of BioGlue® in pericardial sutures and vascular prostheses, its indication still seems controversial in this and other surgery segments[33,34]. Recently, an Austrian group conducted an interesting experimental study comparing the use of GBAA and fibrin sealant in inguinal hernia surgeries. According to the authors, GBAA demonstrated good binding potency, but low biocompatibility (cytotoxicity). They also found persistent inflammatory activity, thus not favoring the use of this material in this specific indication[35]. An experimental study with young pigs on aorto-aortic anastomotic reinforcements also reported persistent inflammatory reaction resulting in stenosis, compromising its indication in children and youngsters[36]. On the other hand, another experimental analysis suggested the use of GBAA as a reinforcer of gastrointestinal anastomoses performed by staplers; however, the authors affirm that more studies are necessary to determine whether or not GBAA is able to prevent or assist in cases of anastomotic fistulas[37]. Complications and doubtful interpretations in imaging methods are also reported in the literature in several surgical areas, including Cardiothoracic Surgery and Neurosurgery[38].

### Cyanoacrylate Adhesives (Dermabond®, Omnex®)

Developed in 1942 by chemist Harry Coover[39] and later marketed as Super Bonder, cyanoacrylates are liquid monomers that rapidly form polymers in the presence of water (hydroxyl ions) and thus quickly glue adjacent surfaces. The property of instant glue made promising the use of cyanoacrylates as adhesives and hemostatic agents, with reports of their use during the Vietnam War cyanoacrylates on open bleeding wounds in an effort to delay bleeding while the wounded soldier was transported to a medical facility.

Ethyl cyanoacrylate, such as Super Bonder, showed to be cytotoxic during degradation (cyanoacetate and formaldehyde), resulting in a marked and persistent inflammatory response, delaying wound synthesis and healing.

Following a restructuring of the molecule into 2-octyl-cyanoacrylate, the product received FDA approval with indication of use in wound repair, marketed as Dermabond®. 2-octyl cyanoacrylate reaches its maximum binding strength within 2.5 minutes of application and forms a stronger and more flexible bond than 2-butyl-cyanoacrylate[1]. In Asia, 2-butyl-cyanoacrylate also found application for embolization of gastric bleeding by direct injection of into the bleeding vessel[1,40]. Although the use of the product in gastroesophageal varices has shown satisfactory results in rapid hemostasis in most cases, its use implies the risk of thrombosis of the mesenteric vein[40]. Case reports describe the use of 2-octyl-cyanoacrylate in interventional radiology for embolization of porto-systemic shunts and anastomotic pseudoaneurysms[41]. Complications related to embolization have also been described and its indication seems to be controversial[42]. Despite cost, the advantages of cyanoacrylates for tissue repair include faster application and repair time, with cosmetic result equivalent to suture results for small incisions and wounds, without the need for follow-up consultation for suture removal.

Another product based on cyanoacrylate and indicated for use in vascular reconstructions and anastomoses is Omnex®. Although there are still few studies on its use, Omnex® has proven safety and efficacy and has been shown to be interesting for vascular and cardiothoracic surgeons, being easy to use, achieving immediate hemostasis when applied and acting independently of the coagulation system[43]. Cyanoacrylate-based adhesives cannot be used to approximate wounds with tissue loss, joint, hand or foot injuries, or to repair dilacerated mucosal surfaces[44]. Cyanoacrylates are becoming increasingly popular for suturing small incisions in the skin, as long as this is a stress-free approach. In addition, as surgeons from different areas have become increasingly comfortable with the properties of these adhesives, cyanoacrylates are subject to more innovative uses and more research.

**Polyethylene glycol (CoSeal®)**

CoSeal® is a fully synthetic polymer used by surgeons to repair areas of potential bleeding in vascular anastomoses. It uses two synthetic polyethylene glycols that, once mixed, can be applied directly to the surfaces of the tissues or used to seal synthetic suture lines or grafts. The sealant works through the interaction of the synthetic products with the human tissue. The polymer remains flexible and is reabsorbed by the body in about four weeks, according to the manufacturer. CoSeal® can increase up to four times its original size. A study conducted by the European Association of Cardiothoracic Surgery showed that patients who received a large application of CoSeal® evolved with cardiac tamponade. Occlusion of the superior vena cava occurred as a direct result of CoSeal® use in one of the 76 studied patients[45]. In this same study, CoSeal® has been shown useful for the prevention of pericardial adhesions in patients who may require surgical reintervention, especially in children suffering from congenital heart disease.

Polyethylene glycol is an effective agent for vascular and cardiac hemostasis or in surgical applications where volume expansion of the product is not a concern. Its performance in the anastomotic seal is equivalent to Gelfoam with thrombin, but the main advantage of CoSeal® lies in the rapidity with which it reaches hemostasis.

## FINAL CONSIDERATIONS

Faced with the heterogeneous family of topical hemostats, the decision on which topical

hemostatic to use and when becomes often confusing. A better understanding of the various types of topical hemostatics and the practical experience gained will allow the surgeon to form an appropriate critical sense to indicate the right agent at the appropriate time. The ideal agent is that easy to use, effective, usable in any or most surgical conditions, non-antigenic, fully absorbable and affordable. We believe that the advancement of bioscience and the realization of new experimental and clinical research will define the hemostatic agent of better cost benefit.

R E S U M O

*A hemostasia tem papel crítico e importância fundamental em todos os procedimentos cirúrgicos. Seu manejo possui diversos pontos chaves, que se iniciam por boa técnica operatória e adequado suporte anestésico. Determinadas situações, como hemorragias graves resultantes de trauma penetrante, por exemplo, não dependem exclusivamente do controle da equipe cirúrgica e necessitam do apoio de novas soluções que diminuam ou controlem a hemorragia. Desde os tempos antigos, um marco da medicina é atuar no controle da hemorragia e, mais recentemente, na facilitação da hemostasia pela aplicação de agentes tópicos, seja por compressão manual ou agentes modernos. Na última década, o número de diferentes agentes hemostáticos tópicos cresceu drasticamente. Para que o cirurgião moderno escolha o agente correto no momento correto, é essencial que conheça o mecanismo de ação, entenda a eficácia e os possíveis efeitos adversos relacionados a cada agente. Assim, a grande variedade de hemostáticos tópicos, somada à ausência de um artigo de revisão na literatura nacional sobre este tópico, nos estimulou a elaborar este manuscrito. Aqui relatamos uma revisão detalhada sobre os agentes hemostáticos tópicos mais comumente utilizados nas especialidades cirúrgicas.*

**Descritores:** *Hemostáticos. Cirurgia Geral. Hemostasia Cirúrgica. Técnicas Hemostáticas. Procedimentos Cirúrgicos Operatórios.*

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