Review

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# Local Hemostatic Agents in Surgical Practice

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ABSTRACT At present, in emergency surgery, great importance is attached to reliable intraoperative hemostasis, for the achievement of which local hemostatic agents are used. The use of these funds tends to increase. The hemostatic agents are divided on 3 main groups. In turn, each group has its own physical and chemical characteristics and different ways of application. The surgeon have task of choosing and correctly using a specific hemostatic agent in a specific clinical situation, especially an emergency one.

Keywords: hemostatic, hemostasis, hemostatic techniques, sealant, fibrin, fibrinogen, vascular surgery

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MFC – microfibrillar collagen
ORC – oxidized regenerated cellulose

## INTRODUCTION

According to the world literature, postoperative bleeding significantly increases the 30-day mortality and worsens the course of the postoperative period in surgical patients [1, 2].

One of the most important problems in emergency surgery is bleeding which occurs both intraoperatively and in the early postoperative period.

Hemostasis plays a leading role in all surgical procedures. In achieving adequate hemostasis, good surgical technique and competent actions of the surgeon aimed at stopping bleeding are of the greatest importance. In addition to the main methods of hemostasis, local hemostatic agents which especially in urgent surgery help achieve more reliable hemostasis have come to the aid of surgeons. They act pointwise and can be used when physical and systemic methods of hemostasis are not effective enough [3]. Recently, a wide range of surgical hemostatic agents have been developed for use in vascular surgery [4, 5]. The specificity of emergency surgical interventions dictates the need for intraoperative use of various hemostatic agents which in turn reduce the risk of postoperative hemorrhage complications. These agents differ widely in their mode of action, composition, method of application, adhesion to wet or dry tissue, immunogenicity and cost.

**Research objective:** to study the literature data on various hemostatic agents used in emergency surgery**.**

## MATERIALS AND METHODS

The literature analysis was carried out in the search engines of PubMed, Google Scholar, ScienceDirect, Scopus, eLIBRARY in English and Russian using the keywords: "Hemostatic", "Hemostasis", "Hemostatic Techniques", "Sealant", "Fibrin", "Fibrinogen ", "Vascular surgery", "Hemostatic agents "," Local hemostasis". More than 150 sources were reviewed from 1970 to 2019. The review included studies which evaluated various hemostatic agents, patterns of their use, comparative qualities, and their impact on the postoperative period.

## RESULTS

According to the analysis of the data obtained, local hemostatic agents can be divided into three broad categories: absorbent agents, biological agents associated with the coagulation cascade, and synthetic adhesives.

### ABSORBENT AGENTS

**Oxidized regenerated cellulose (ORC)**

Ordinary oxidized cellulose as a local hemostatic agent was first proposed in 1942 in the USA. In 1960, a new local hemostatic agent, ORC, appeared on the market [6]. It is a sterile, ready-to-use hemostatic film composed of two components: polyuronic acid and a fibrous component (cellulose). ORC is easy to use in surgical procedures due to its loose woven cotton-swab-like material (Surgicel Fibrillar®, Gelitacel®, Willocell Fibril®), a small piece of mesh (Surgicel Nu-Knit®, Willocell Standard®, Emosist®) which acts as a support matrix for the initiation and formation of a clot, or in the form of a composite (Oxycelodexum®) consisting of oxidized cellulose powder, polyglucin and water.

The use of cellulose is associated with a decrease in local acidity. Low pH causes primary local hemostatic action and secondary activation of platelets with the temporary plug formation [7]. Low acidity also creates conditions in which most bacteria cannot survive [8]. Antimicrobial activity against major organisms associated with wound infection was noticed. Evidence suggests that antibiotic resistant microorganisms are susceptible to the antimicrobial activity of ORC. When tested 9 out of 10 bacterial species, including drug-resistant strains (*VRE, MRSA* and *PRSP*), there was a sharp decrease in the number of colonies after 24-hour exposure [9].

The disadvantage of low pH is the inactivation of biological active coagulants such as thrombin. As a result, ORC cannot be combined with other biological hemostatic agents. There is also some evidence that low pH slows down the physiological healing process [10].

Biodegradation of ORC in the body occurs due to the breakdown of two components. Polyuronic acid is depolymerized within an average of 18 hours after implantation, which is facilitated by glycosidases, and the fibrous component is phagocytosed and then hydrolyzed by local macrophages [11, 12]. The oxidation process makes cellulose sensitive to glycosidases, but also gives oxidized cellulose its hemostatic and bactericidal properties. Complete dissolution of ORC takes from 2 weeks to several years, depending on the amount of the material used [10].

Currently, ORC-based materials are used in cardiovascular surgery, traumatology, neurosurgery, general surgery, oncology, gynecology and ENT surgery to stop capillary, venous and minor arterial bleeding [13, 14]. From domestic medications, Oxycelodexum® can be mentioned, a powdery product which is widely used in surgical dentistry and minimally invasive interventions.

**Gelatins**

The first gelatin-based sealant was applied in 1945 (Gelfoam®, Baxter Healthcare), it was a hemostatic agent made from hydrolyzed and purified animal collagen (cattle, pigs, sheep).

Sealants of this type are highly absorbent and provide a mechanical matrix for clot formation. They act at the final stage of coagulation cascade, promoting fibrin formation and minimizing blood loss [15].

The gelatin matrix is used in various forms: sponges (Spongostan®), powders (Gelplastan®), sterile solutions.

Unlike ORC, the pH of the gelatin matrix is neutral and therefore gelatin can be used in combination with thrombin or other hemostatic agents to enhance the hemostatic effect. Attention should be paid to using the minimum amount of the substance to achieve hemostasis and remove excess product once hemostasis is achieved.

Gelatin absorbs 40 times its weight in blood and increases *in vivo* by 200%. This property provides a good mechanical hemostatic effect, but when used in a limited cavity or near nerve structures in the case of spinal surgery, gross neurological complications may occur [16–19]. Neurotoxic reactions are also possible in the form of anorexia, anxiety, nausea, confusion and depression [20]. The gelatinous matrix is absorbed within 4-6 weeks.

The advantages of gelatin are low cost, ease of storage (at room temperature) and ease of use.

A major breakthrough in the field of gelatin matrix hemostatic agents is associated with the development of a product called Floseal®. Unlike other (absorbing agents) hemostatics with a gelatin matrix, Floseal® is a gelatin matrix based on microgranules containing bovine collagen in combination with glutaraldehyde which acts as a semisynthetic adhesive, and a solution of human thrombin, which are mixed during use [21, 22 ]. This feature allows it to be more effective in controlling moderate bleeding compared to other agents. It is versatile and can be adapted to a variety of surfaces, including actively bleeding vascular anastomoses. *Nasso G. et al.* (2009) conducted a retrospective study of the efficacy of Floseal® in cardiovascular surgery, in which it was compared with other hemostatic agents [23]. The results of this study showed that with Floseal®, the rate of successful hemostasis is higher compared to other topical hemostatic agents. This contributed to decreased number of patients requiring blood transfusion, and, if necessary, blood transfusion was performed in much smaller volumes [24]. Studies in other areas of surgery such as orthopedic surgery, liver surgery, gynecological surgery and urology have shown similar results. The use of Floseal® in surgery has been demonstrated to be safe and effective [25–27].

**Microfibrillar collagen (MFC)**

Collagen as a hemostatic agent was developed and first used in 1970 in the United States [28]. It was obtained by purifying the collagen fiber of cattle. MFC products are soft, but not friable, in structure, white, plastic.

They are used in the form of powders (Avitene®), cloth-like materials, sponges or small pads (Instat®). For its activation, MFC requires direct contact with the bleeding tissue structure [29, 30].

Collagen-based derivatives activate the intrinsic pathway of the coagulation cascade, while gelatins induce hemostasis through physical properties. In randomized clinical trials, MFC outperform ORC, demonstrating a statistically significant reduction in blood loss [31]. After the application of MFC, platelet adhesion and activation occurs within 2–5 minutes [32].

Given the mechanism of its action that depends on platelet activation, MFC is less effective in patients with severe thrombocytopenia and coagulopathies. However, its effect is much better expressed than that of other materials during deep heparinization of patients [33]. For this reason, it is more often used in vascular surgery for profuse bleeding [30]. Unlike gelatins, collagen does not increase in volume and is absorbed in less than 4 weeks [34].

In 2013, the COBBANA single-center randomized trial compared MFC (Lyostypt®) and ORC (Surgicel®). According to the results of this study, the duration of bleeding after using MFC was 3.5 times less than after using ORC. In 27 cases out of 32, hemostasis with the help of MFC was achieved within 3 minutes, compared with 8 minutes after applying ORC. Also, the researchers note that MFC is more economically feasible due to the use of a smaller amount of the substance [35].

Microfibrillar collagen can cause allergic reactions associated with animal antigens. Also, the disadvantages include the need to apply the hemostatic agent with a dry instrument, since it tends to stick to gloves. The advantages of collagen hemostatic agents include rapid hemostasis, the need for a small amount of material to achieve it, as well as the possibility of their removal from the site of application without the risk of renewed bleeding due to the fact that the coagulation cascade has already been initiated. Currently, surgeons use MFC in small volumes, in particular in neurosurgery and cardiovascular surgery.

## BIOLOGICAL AGENTS ASSOCIATED WITH THE COAGULATION CASCADE

### Fibrin sealants

Fibrin sealants were first mentioned in historical reports in 1909 in Europe. More active research continued in the 1940s after the availability of purified thrombin and its use became common in various surgical specialties. In the 1980s, one of the first representatives of this group of sealants (Tisseal®) was approved for use and has shown its effectiveness and safety [36].

The fibrin sealant is a biological adhesive that imitates the final stages of clotting and forms a fibrin clot. The classic fibrin sealant consists of lyophilized human fibrinogen and bovine or human thrombin, sometimes also containing coagulation factor XIII concentrate and aprotinin [37]. Factor XIII is a proenzyme activated by thrombin in the presence of calcium ions (fibrin-stabilizing factor), and after its activation, bonds are formed between fibrin chains thus stabilizing the formation of a clot.

Thrombin has a significant effect on the rate and nature of coagulation, helping to reduce intraoperative blood loss, the volume of intravenous infusions, and the need for postoperative drainage [38]. Aprotinin is a derived from bovine lung serine protease inhibitor that inhibits trypsin, plasmin and kallikreins, delaying plasmin-mediated clot lysis.

The use of fibrin glue for a higher effect usually requires a dry working field. Fibrin glue is most effective when used before bleeding. In this situation, the adhesive polymerizes before blood pressure increases local blood flow in the vascular anastomosis, thereby increasing pressure on its walls. Application of fibrin glue after the onset of bleeding requires manual compression of the bleeding area [39].

Collagen matrix induces platelet aggregation and stimulates coagulation factor XII. On contact with liquid, the solid components dissolve and form a viscous fibrin clot between the matrix and the untreated wound surface. A compression period is required for the sealant components to cure.

Combinations of fibrin or thrombin with cellulose, gelatin or collagen (Surgiflo®: gelatin + thrombin) were developed to increase the effectiveness of local hemostatic agents. These products combine the mechanical effects of absorbent agents and the hemostatic effects of a fibrin sealant.

Fibrin sealants that do not require compression can be made with hydrophilic particles that grow in size, dissolve in a liquid matrix, and adhere to surgical wounds (Floseal®). This type of sealant does not require a dry surgical field to be applied. Other sealants (CoStasis®, Vitagel®) consist of a microfibrillar compound of collagen and bovine thrombin mixed in a syringe with patient plasma taken during surgery. Plasma components release fibrinogen which is cleaved by thrombin to form a gelatinous collagen-fibrin matrix [40]. The use of the patient's plasma requires the involvement of additional human and instrumental resources which can potentially affect the duration of surgery.

In 2003, Crosseal® was developed, the distinguishing feature of which is that it consists only of products of human origin (fibrinogen and plasma thrombin, as well as tranexamic acid) [41]. In 2004 *Schwartz M. et al*. (2004) reported that, in a multicenter, prospective, randomized study, Crosseal® / Quixil® was the most effective hemostatic agent with less time for effective hemostasis, less intraoperative bleeding and less induction of complications compared to the control group (Avitene®, Surgicel®, Surgicel NuKnit ®, Gelfoam, Gelfoam + thrombin) [42].

Another sealant on the market is Evicel® which is free of fibrinolytic inhibitors and requires minimal preparation time before use, making it easy to apply. It can be used in spray form, demonstrating satisfactory hemostasis. Tisseel®, Quixil® and Evicel® fibrin adhesives are especially suitable for combating bleeding at low venous pressure.

The disadvantages of fibrin are as follows: higher risk of hypersensitivity reactions, the possibility of transmission of infections from blood donors and insufficient clot strength [43]. When using fibrin glue on a small diameter anastomosed vessel, over-application is difficult to avoid. The latter causes hardening of the vessel wall and intraluminal thrombosis. When using glue, it is necessary to first apply the first component, then the second, or simultaneously apply both using the duploject system device (Fig. 1) (a cassette for 2 syringes with a common plunger) and an application needle (short blunt needle, at the base of which stirring occurs) [43].

Fig. 1. Appearance of the “DUPLOJECT” system

**Thrombin**

Thrombin is a natural clotting factor of the intrinsic and extrinsic coagulation pathways.

At the moment, only recombinant human thrombin is used in surgical practice, which causes significantly fewer complications in the form of hypersensitivity reactions and contributes to the formation of a denser clot base. It is used in combination with absorbent agents or other biological agents that affect the coagulation cascade. One of the combination products is TachoComb®.

The TachoComb® hemostatic sponge consists of horse collagen, bovine thrombin, bovine aprotinin and human fibrinogen [44]. Currently, the third generation of this product (which in Europe is called TachoSil®) is presented on the Russian market. The manufacturers changed its composition and removed bovine thrombin (replacing it with human thrombin) and aprotinin, since it could cause immunogenic and anaphylactic reactions [45]. When applied to bleeding tissue, it initiates the final step of the natural coagulation cascade, creating a fibrin clot at the site of application; it takes 3-5 minutes to achieve a hemostatic effect. Clinical studies conducted in Europe have shown that TachoComb® provides effective hemostasis for liver resection and has a high level of safety and tolerability [46–48]. One of the greatest advances in the third generation TachoComb® over its predecessors is its ability to be stored at room temperature. Its biodegradation under the impact of tissue enzymes occurs in about 24 weeks [49].

A multicenter study which involved 3098 patients in 227 different centers showed that the use of Tachocomb decreased the duration of surgery in 55.5% of patients by 12.2 ± 13.1 minutes compared with the use of other methods of hemostasis, and also reduced the need for transfusion of blood components in 13.5% of patients [50].

Systematic review of *Colombo G.L. et. al.* showed the economic benefit of using the Tachocomb - for example, the length of stay in a hospital after surgery using this product is reduced by 2.01–3.58 days in comparison with the results of standard methods of hemostasis, which leads to a decrease in treatment costs [51].

## SYNTHETIC ADHESIVES

**The sealant composed of bovine serum albumin and glutaraldehyde**

The glue based on these substances is used as additional hemostasis in operations on large blood vessels, since its distinctive property is to create a dense bioactive film that is able to withstand the high bursting pressure characteristic of large magistral vessels. It is undesirable to use the glue on small vessels, as this can lead to a number of complications, including thrombosis, embolism and necrosis of the surrounding tissues. After application, the glue completely polymerizes and fixes the tissue in 2-3 minutes.

The most commonly used adhesive in this group is BioGlue®, which has been successfully used in the surgery for large blood vessels. BioGlue® is a two-component adhesive consisting of a 10% gluteraldehyde solution and a 45% purified bovine albumin solution [52]. It has been used in clinics in Russia since 2005.

The authors of a study published in 2001 comparing the hemostatic efficacy of Bioglue® versus Surgicel® in sheep concluded that Bioglue® may be beneficial for patients with coagulopathies and those who underwent repeated vascular interventions. In this study, descending thoracic aortic bypass surgery was performed after all the animals received heparin and aspirin. Bioglue® has been shown to be more effective in preventing blood loss than Surgicel®. The inflammatory response was minimal in sheep treated with Bioglue® 3 months after surgery [53].

BioGlue® is not recommended for pediatric use, as the biofilm formed is not elastic, which further leads to the formation of stenosis at the site of its application, impaired growth and tissue formation.

**Cyanoacrylate adhesives**

Cyanoacrylates were first synthesized in 1949. In the 1960s, their adhesive properties were described and their potential use as surgical adhesives was proposed [54–55].

They are synthetic fabric adhesives consisting of a mixture of two monomers: 2-octyl cyanoacrylate and butyl lactoyl cyanoacrylate. The substances that make up the glue are liquid monomers that quickly form polymers in the presence of liquids and, as a result, bond tissues. The adhesive polymerizes in the form of a film that adheres to tissues and / or synthetic materials and creates a flexible physical plug, the formation of which is independent of the coagulation cascade. The polymerization time is about 2 minutes [56].

Omnex® (Fig. 2) is a cyanoacrylate based adhesive for use in vascular reconstructions. This product was researched in a small number of studies, but has proven its safety and efficacy, and it was shown to have potential for use in vascular surgery, it is easy to use, provides immediate hemostasis and acts independently of the coagulation system [56].


Fig. 2. Appearance of the system for the introduction of Omnex® cyanoacrylate adhesive

When using the adhesive, it is necessary to take into account the allergic history, since it is prohibited for use in patients with known hypersensitivity to cyanoacrylate and formaldehyde due to the risk of severe anaphylactic reactions.

**Polyethylene glycol**

Polyethylene glycol consists of two synthetic polyethylene glycols, dilute hydrogen chloride solution and sodium phosphate / sodium carbonate solution. After mixing these substances, the resulting glue can be applied to damaged areas, the maximum hemostatic effect occurs within 2 minutes [57]. The sealant works by the interaction of synthetic products with human tissue.

CoSeal® is a fully synthetic polymer used by surgeons to repair areas of potential bleeding during vascular anastomoses. It consists of two synthetic components, which, after mixing, can be applied directly to the surface of tissues or used to seal synthetic suture lines and grafts. The sealant works through the interaction of the synthetic products with human tissue. According to the manufacturer, the polymer remains flexible and is absorbed by the body in about 4 weeks [57].

CoSeal® is able to increase by 4 times compared to the original size, which can have both negative effects in the form of a compressive effect on the surrounding tissues, and a positive one - in the form of complete sealing of the injection sites and the suture line itself [57].

There is also a study by *Natour E. et al.* (2012) performed on 12 dogs which underwent polytetrafluoroethylene arterial grafting to test the efficacy of CoSeal® as a hemostatic agent. One end of the graft was treated with CoSeal®, while hemostasis of the other end (control) was carried out by plugging with gauze and mechanical compression. The advantage of using CoSeal® was evident: the time to complete hemostasis was 5 minutes with CoSeal® versus 15 minutes for the control end. Blood loss was lower at the Coseal® treated end (19 g versus 284 g on the control end). However, histological examination showed moderately pronounced inflammation in the area of CoSeal® application on the 7th, 30th and 60th days [58].

Another study related to the use of CoSeal® was carried out in Germany: 6 surgeons performed aortic repair in 124 patients. Three of the surgeons used CoSeal®, while the other three did not. The surgeries included total aortic root replacement, reconstruction or total replacement of the ascending aorta, and interventions on the aortic arch. CoSeal® was applied to the seam line and allowed to dry. It was demonstrated that the CoSeal® group required less fluid therapy (e.g. erythrocytes: 761 packs versus 1248 in the control group; fresh frozen plasma: 413 versus 779 in the control group; there was a decrease in drainage losses in the postoperative period: 985 ml when using CoSeal® versus 1709 ml in the control group). In addition, fewer CoSeal® patients required repeat sternotomies (1 in 48 in the CoSeal® group versus 6 out of 54 in the control group), and the patients also spent less time in the intensive care unit [59].

Thus, polyethylene glycol synthetic adhesives have great potential for use in vascular surgery due to effective stopping of bleeding, adequate control of hemostasis in the postoperative period, and a decrease in blood loss during operations on large major vessels which in turn reduces the amount of infusion load and the duration of intensive therapy.

**Polyacrylic acid**

Hemoblock® is a new versatile hemostatic agent that consists of silver salt of polyacrylic acid and silver nanoparticles (Fig. 3). It has an antiseptic and bactericidal effect, expressed against known strains of bacteria, including resistant nosocomial strains. Hemoblock® has a liquid form and to achieve hemostasis is applied directly to the wound surface or using sterile gauze or cotton swabs for parenchymal and capillary bleeding. The hemostatic effect is achieved through interaction with blood albumin and the subsequent formation of an elastic clot; it takes 1-2 minutes to achieve hemostasis.

According to a single-center, blind, randomized trial performed by *Degovtsov E.N. et al.*, Hemoblock reduces the duration of postoperative wound drainage, the number of exudative complications, the risk of seromas and infections in the surgical site, as well as the severity of pain and the need for analgesics [60].


Fig. 3. Appearance of Hemoblock® hemostatic solution

The results of a single-center non-randomized study presented by *Tereshchenko S.G. et al*. [61], which included 205 patients who underwent laparoscopic gastric endoscopic polypectomy, showed that with the development of bleeding from a thermal defect, the use of endoscopic irrigation or infiltration of the base of the polyp with the hemostatic Hemoblock® allows achieving reliable hemostasis in early and late post-polypectomy bleeding, which reduces the number of emergency operations.

Taking into account the data presented, it can be assumed that Hemoblock® during open surgical interventions can be used interoperatively in order to improve mechanical and thermal hemostasis.

There are also data from *Andreev A.I. et al.,* testifying that the hemostatic effect of Hemoblock® is achieved in any way during abdominal and laparoscopic surgical interventions without infectious complications [62].

The analysis of the few studies of this product requires further research of its properties and indications for use, but there is already a clear trend towards potential high efficiency in the field of wound hemostasis.

It can be concluded that this agent has features that are important for surgical practice. The product has a liquid form which facilitates its application to biological tissues, and does not require special preparation, which is very important in urgent surgery. The positive side of Hemoblock® is also the fact that when it is applied to bleeding tissue, the visualization of the boundaries and location of the defect is not disturbed.

When studying the literature related to Hemoblock®, there is no mentioning of its use in vascular surgery, but its biological properties, level and degree of influence on hemostasis potentially satisfy most of the requirements for a hemostatic agent in vascular surgery.

Thus, the presence of a wide range of hemostatic agents dictates the need for the operating surgeon to be well oriented in them in order to clearly define indications and contraindications, as well as specific clinical situations in which these products are needed [63].

## CONCLUSOIN

Currently, the use of local hemostatic agents is gaining popularity, as they have proven to be effective and safe. They are ideal products — simple, effective, suitable for virtually any surgical setting, non-antigenic, fully reabsorbable, and affordable. But a versatile product that would have all the positive qualities of an ideal hemostatic agent does not currently exist, therefore, when using them, the surgeon must be guided by the specific clinical situation.

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