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# МЕСТНЫЕ ГЕМОСТАТИЧЕСКИЕ СРЕДСТВА И ПУТИ ИХ СОВЕРШЕНСТВОВАНИЯ

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В последнее время за рубежом и в нашей стране всё большее распространение получают местные гемостатические средства (МГС). Они действуют направленно и могут быть использованы как при повреждении крупных сосудов, так и при диффузном кровотечении. В статье рассматриваются химическая природа, физико-химические характеристики материалов и механизмы активности МГС, возможные направления их совершенствования. МГС чаще всего классифицируют по механизму действия.

На сегодняшний день популярными группами являются «мукоадгезивные агенты» (хитозан, амилопектин) и «концентраторы факторов свертывания» (цеолиты, каолин). Также выделяют группу «стимуляторы агрегации и адгезии» (коллаген, целлюлоза). При этом, представители вышеуказанных групп имеют общие характеристики – очень высокую пористость и гидратационную способность. Еще одна группа объединяет вещества, «способствующие денатурации белков» (неорганические соли металлов, а также соли акриловой кислоты и ее производных). Полиакрилаты также являются основой клеев с гемостатической активностью. Однако, большинство современных МГС являются комплексными и именно эта группа является наиболее перспективной. Все средства, начиная от гемостатических губок производства Зеленая Дубрава (Россия) и Nycomed, Такеда (Австрия, Норвегия), до гемостатических материалов производства MedTrade (Великобритания), Etiguette и Z-Medica (США), сочетают в себе сорбционные и собственно тромбообразующие свойства. Часто под торговыми марками скрываются оригинальные композиции и, тем более, технологии: Quick Relief, BioSeal, BallistiClot, Hemaderm, CELOX Gauze PRO, OMNI-STAT Hemostatic Gauze for minor external bleeding. Наиболее эффективными признаны МГС на основе хитозана и каолина в форме повязок, обработанных тромбоформирующим средством, например искусственными тромбоцитами или другими факторами свертывания.

***Ключевые слова:*** *местные гемостатические средства; гемостатические губки; цеолиты; хитозан; метилцеллюлоза; коллаген; желатин.*

# LOCAL HEMOSTATIC AGENTS AND WAYS OF THEIR IMPROVEMENT

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Recently, local hemostatic agents (LHA) have become increasingly popular abroad and in our country. They act in a targeted way and can be used both in damage to large vessels and in diffuse bleeding. In the article, chemical nature, physical and chemical characteristics of materials and mechanisms of LHA activity are considered, directions of their improvement are shown. LHA are mostly classified by mechanism of action.

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To date, the popular groups of hemostatic agents are «mucoadhesive agents» (chitosan, amylopectin) and «coagulation factors concentrators» (zeolites, kaolin). Other authors distinguish the group of «aggregation and adhesion stimulants» (collagen, cellulose). Here, representatives of these groups have common characteristics – very high porosity and hydration ability. Another group includes substances that «promote protein denaturation» (inorganic salts of metals, as well as salts of acrylic acid and its derivatives). Polyacrylates are the basis of adhesives with hemostatic activity. However, most modern LHA are complex drugs and it is just this group that is most promising. All means, from hemostatic sponges produced by Zelyonaya Dubrava (Russia) and Nycomed, Takeda (Austria, Norway), and to hemostatic materials of MedTrade manufacture (Great Britain), Etiguette and Z-Medica (USA), combine sorption and, actually, thrombotic properties. The trademarks often imply original compositions and, especially, technologies: Quick Relief, BioSeal, BallistiClot, Hemaderm, CELOX Gauze PRO, OMNI-STAT Hemostatic Gauze for minor external bleeding. The most effective LHA are those based on chitosan and kaolin in the form of dressings with embedded clot-forming substance, for example, with artificial platelets or other coagulation factors.

***Keywords:*** *local hemostatic agents; hemostatic sponges; zeolites; chitosan; methylcellulose; collagen; gelatin.*

There exist many methods of arresting capillary-parenchymal bleeding – compression of the liver or spleen tissue with a clamp or catgut mesh, application of hemostatic sutures, and other physical and pharmacological methods of hemostasis. Recently, local hemostatic agents (LHA) referred to «sparing» means of blood arrest have been gaining popularity both in Russia and abroad [1]. They act in a targeted way and can be used in damages to large vessels and in diffuse hemorrhages (parenchymal organ, cancellous bone) when physical and systemic methods of hemostasis appear non-effective [2].

Application LHA are produced in different forms: gels, adhesions, woven and nonwoven materials, hemostatic sponges, solutions and powders. The aim of all LHA known today is imitation of specific processes of natural hemostasis, their acceleration or a rapid formation of a fibrin clot by some other mechanism [3]. Here, *a hemostatic agent that fails to stop diffuse bleeding within two minutes, should be considered non-effective* [4].

*By the mechanism of activation of hemostasis, the local hemostatic agents, or hemostats, are classified into passive, active, fluid agents and sealants* [5]. Passive agents trigger a natural cascade of clot formation through sorption and aggregation, they include collagenous drugs, drugs on cellulose and gelatin basis. Active hemostatic agents contain components of clot formation cascade. Two other categories – fluid hemostatic agents and sealants include fibrin adhesives, polymers of polyethylene glycol (PEG), albumin, glutaric aldehyde and cyanoacrylate. Besides, there also exist *absorbing, biological, synthetic dressings* [6]. Modern hemostatic materials used in surgical practice, are classified into two groups by mechanism of hemostasis: *those accelerating local chemical hemostasis and those performing the role of physical (mechanical) agents starting aggregation of platelets*. A representative of the first group most popular among surgeons is microfibrillar collagen, and in the second group the preference is given to gelatin sponges, oxidized cellulous fiber and amylopectin

*By mechanism of activity,* local hemostatic agents are categorized into:

- vasoconstrictors and pro-aggregants;
- plasma coagulation factors;
- inhibitors of fibrinolysis;

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Table 1

*LHA Included into Register of Medical Remedies of Russia in 2018*

| Basic Material | Added Components | Tradename (Company, Country) |
|---|---|---|
| Collagen | + platelets | Trombokol (Belkozin plant, Luga, Russia)<br>KollapApan (OOO Intermediapatit, Russia) |
| | +furacilin+boric acid | Collagen sponge (OAO Belkozin plant, Luga, Russia) |
| | +methyluracil | Meturakol (OAO Belkozin plant, Luga, Russia) |
| | +platelets+plant antiseptic sang-viritrin<br>+ +gentamycin | Trombokol-AS<br>Trombokol AG (OAO Belkozin plant, Luga, Russia) |
| | +thrombin<br>+fibrinogen+albumin+sodium chloride+sodium citrate<br>+riboflavin | TachoComb (Takeda Austria, Norway) |
| | + degestase enzyme (collagenase) | 3AO Zelyonaya Dubrava, Russia) |
| | +colloid silver or lincomycin / gentamycin / metronidazole /klaforan, dioxydine / rifampicin / isoniasid | KollapApan-S, KollapApan-L, KollapApan-G, KollapA-pan, KollapApan-K, KollapApan-R, KollapApan-D, Kolla-pApan-I (OOO Intermediapatit, Russia) |
| Gelatin | | Spongostan (Johnson & Johnson, USA),<br>Surgiflo (Johnson & Johnson, USA) |
| | + kanamycin | Zhelplastan (Tanais, Russia) |
| Chitosan | | HemCon (Hemorrhage Control Technologies Inc., USA)<br>Celox (MedTrade, Great Britain)<br>Hemofleks Combat (OOO Inmed, Russia) |
| Oxidized cellul-ous fiber | | Surgicel (Johnson & Johnson, USA) |
| Amylopectin<br>Alginic acids | sodium alginate+furaginum | Hemostatic bandages Koleteks-SAFG-Gem (OOO Kole-teks, Russia) |
| | calcium alginate+oak tree bark,nettle, St. John wort, bottlebrush extracts | Polihemostat (OOO Tekhnopark-Center, Russia) |
| Zeolite | | QuikClot (Z-Medica, USA)<br>Hemostop (НПЦ Farmzashchita, Russia) |

• stimulators of aggregation and adhesion;

• promoting protein denaturation;

• mixed [2,7].

Recently, Russian and international manufacturers supply many materials of local application to the market. In 2003 US Military Forces started using local hemostatic agent on the basis of synthetic zeolite QuikClot (Z-Medica, USA), which was followed by a drug based on chitosan (Hemorrhage Control Technologies Inc., USA). These agents, respectively, served the basis for development of two LHA groups – concentra-

tors of coagulation factors and mucoadhesives capable of sticking to mucous membrane [8]. These two groups are supplemented with a group of procoagulant agents [1].

In the periodical literature there is much discussion of a choice of methods of hemostasis, of a hemostatic agent and of probable mechanisms of their action. Here, hemostatic agents are usually described not by classification principle, but by the substance they contain – fibrin-containing, cyanoacrylates, agents containing cellulose, collagen, gelatin, etc.

The given work considers a chemical structure and physico-chemical characteristics of LHA materials. In most cases it is a biodegradable material adapted to living tissue. In the work, patented names and characteristics of hemostatic agents widely discussed in literature, are used. LHA included into Register of Medical Remedies of Russia 2018, are given in Table 1.

Let us consider hemostatic means according to their chemical structure.

***Hemostatic Drugs of Protein Origin***

*Collagen* is protein that makes the basis of connective tissue of animal organisms. Structural and chemical stability of collagen, its physical peculiarities are provided by unique organization of three-spiral macromolecules which, at physiological temperature, pH and ionic strength, undergo aggregation with formation of a three-dimensional mesh of intermolecular bonds of different origin. In contact with the «loops» of collagen spirals the entering molecules and cells form inclusions (clathrates). Collagen accelerates the natural way of coagulation and starts blood coagulation process when fibrils of the material come into the first contact with platelets. Aggregated platelets undergo normal morphological changes, in particular, degranulation, with release of ADP, serotonin, thromboxane $A_2$ that help in clot formation. Thus, the main hemostatic mechanism of collagen consists in aggregation and activation of platelets.

Dispersed collagen in the concentration above 0.5% forms stable emulsions of M/B type. In dehydrating conditions, non-brittle transparent films are formed from a thin dispersion layer, and in spray drying – powders. The production technology of a collagen sponge is based on the method of lyophilization of a thin layer of collagen solution. In the process of sublimation of crystals of frozen water in deep vacuum, highly-porous sponges are obtained in which the volume of through and dead-end pores makes 50-90% of the total volume of a sponge. Such a sponge possesses a high sorption property and accommodates the amount of moist many times exceeding its weight, almost without enlargement in size. Hemostasis takes 2-5 minutes. Collagen forms water- and air-proof gel-like layer; however, the sponge plate should be tightly pressed against the wound surface (the preparation poorly adheres to rough wound surface because of rigidity of collagen fibers). Collagen sponges prove effective only in moderate parenchymal bleedings. In massive mixed bleedings they are «swept away» from the wound surface. In an organism collagen undergoes enzymatic breakdown with a complete resorption period 4 weeks. In *in vivo* experiment, a friable mass forms at the site of the plate, and the adjacent tissues have elements of moderate inflammation. Later, the plate material is replaced and in histological examination looks like connective tissue or an area of sclerosis [9].

Most modern LHA based on collagen, contain substances that influence certain stages of blood coagulation [4]: platelets (Trombokol), thrombin, fibrinogen (TachoComb), epsilon-amino capronic acid, hydroxyapatite, etc. In interaction of collagen with calcium-containing solutions, cations tightly bind when entering triple helix, and it changes the conformation in such a way that water molecules are no longer held by this portion of the triple helix. This causes local loss of water and «cross-linking» of the structure with for-

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mation of a more solid spongy material. Organic cations – alkaloids, like heavy metal ions, are stereochemically bound by collagen, while low- and non-ionized substances do not form strong bonds. This property permits to control the activity of medical drugs in the structure of collagen-containing forms.

The most popular in Russia «Hemostatic collagen sponge» (Belkozin, Luga, Russia) contains furacilin and boric acid antiseptic drugs. The most popular international hemostatic agent in Russia is fibrin-collagen biopolymer TachoComb [10] that consists of a collagen plate covered on one side with highly concentrated thrombin, fibrinogen and aprotinin. After contact with a bleeding wound or other fluids, blood coagulation factors dissolve and create bonds between a carrier – collagen and the wound surface. TachoComb possesses the ability to seal the surface which is necessary in certain cases. Its Russian analog is Trombokol sponge [11].

*Gelatin* is a product of a partial destruction of collagen. Like collagen, it provides a physical matrix for initiation of blood coagulation. Gelatin effectively controls bleeding from small vessels and is recommended for use as a hemostatic plug wrapped in oxidized cellulose. pH of gelatin sponges approaches 7 which makes it possible to use them in combination with thrombin or with other substances for enhancement of hemostatic action. Gelatin granules permit concentrated thrombin to rapidly react with patient's fibrin to form a mechanically stable fibrin clot. As soon as blood impregnates gelatin matrix, granules of the agent swell 20% in 10 minutes restricting leakage of blood and providing soft tamponade that conforms the form of the wound. The formed clot is resorbed within 6-8 weeks. A disadvantage of gelatin-based means is a probability for embolism in case of their getting into a vessel, and compression of tissues by swelling in case of sealing of the wound. Besides, gelatin should not be used for closure of skin cuts because getting of gelatin into a cut may prevent connection and healing of the edges of the skin wound. The main disadvantage of gelatin is its easy contamination with bacteria, due to which it can become a focus of infection.

Gelatin product may have different consistency. For example, Spongostan of a fine powder. For effective application it is mixed with saline to obtain a loose mass which may be applied with hands or with an applicator, Surgiflo is made of pig gelatin and is a fluid foamy mass. It is used in the form of gel with which hard-to-reach bleeding places and cavities are treated. In mixing with saline and body fluids it expands in volume. Gelatin sponge Spongostan is made of neutralized gelatin foam, it is not used in infected areas or should be eliminated from them after hemostasis; insoluble in water, but completely resolves within several weeks. In histological examination may resemble suturing materials [9].

In Russia, Zhelplastan preparation is registered (Patent 2067447 RU) - a powder substance with hemostatic activity. Treatment of experimental gastric ulcers with Zhelplastan in combination with granulated sorbent – diovin – accelerates ulceration phases and reliably accelerates repair of gastric tissues [12]. The given LHA owes its effectiveness to sorption (absorption of fluid and concentration of clotting factors) and adhesion (initiation of coagulation) properties of powders with no damaging effect on tissue.

*Polysaccharides.* High-molecular carbohydrates are long linear or branched chains of monosaccharide residues linked with glycoside bond. As hemostatic agents cellulose, chitin (in nature they perform structural functions), starch (reserve function), and other substances are used.

An advantage of cellulous fiber materials is their existence in different forms: tissue (gauze), non-woven and knitted fabric, cotton wool, etc. Gauze possesses a high adhesion to wound; but high hygienic, sorption and physico-mechanical properties of ban-

dages on the basis of cellulous fibers can neither be denied. Woven and non-woven materials are most common carriers of hemostatic factors of the following groups: plasma coagulation factors, vasoconstricting and proaggregation agents, inhibitors of fibrinolysis, etc.

After chemical modification cellulose acquires physiological activity of its own which permits its use as a therapeutic form without addition of medical drugs. Thus, carboxymethyl cellulose containing functional groups of acid type is capable of binding peptides in the wound, in particular, elastase, and thus can suppress its activity. A well-known material is monocarboxy cellulose used as blood-arresting gauze. A high biological inertness of carboxymethyl cellulose permits to use it as a barrier means for instance, in the form of hydrogel (Mesogel) for prevention of adhesive processes in the abdominal cavity. Na-carboxymethyl cellulose possesses a pronounced stimulating effect on reparative processes, accelerates formation and maturation of granular tissue and produces an active effect on fibrillogenesis. Na-carboxymethyl cellulose powder swells and forms transparent gels and viscous gel-solutions that form films after drying off. These transformations of carboxymethyl cellulose are effectively used in hemostasis.

*Oxidized methyl cellulose* in local application absorbs blood, promotes formation of a platelet and later on of a fibrin clot. The material has a cotton-like consistency and does not adhere (Patent №2563279 RU). Oxidized cellulose acts as a caustic substance bringing an artificial component of clot formation into hemostasis. Contact with moist medium triggers degradation process with release of cellulous acid and reduction of the local pH. Low pH of oxidized cellulose induces vasoconstriction with simultaneous lysis of erythrocytes. Hemoglobin released from erythrocytes reacts with cellulous acid to form acid hematin. This explains a change of color of the hemostatic agent in the wound from the initial white or yellowish to brown at the moment of interaction with blood. On the other hand, low level of pH promotes coagulation necrosis which considerably restricts application of oxidized methyl cellulose as hemostatic agent. The material usually dissolves turning into gel-like substance which covers the area of damage of blood vessels and completely resolves in 1-2 weeks, without histologically detected traces of its presence in tissues.

LHA based on oxidized regenerated cellulose Surgicel Fibrillar is non-woven 7-layer material that does not break up in cutting, has a good adhesion to tissues; its fibrillar structure easily models the size and shape of the fragment. It can be applied as a whole, in layers, in bundles and turundas and therefore is convenient for use in hard-to-reach places. The average time for blood arrest is 2-4 minutes.Polymers of a group of *nitrogenous polysaccharides*: chitin (N-acetyl glucosamine) and chitosan (N-deacetylated glucosamine) have been widely used in medicine since the early 2000s [13], although they had been known to science for about 200 years. Chitosan, unlike chitin, is not degraded in an organism by specific enzymes. Absence of biodegradation in chitosan is compensated for by its polyelectrolyte properties – formation of gels with abnormally high viscosity in reduction of polymer concentration. Chitosan forms strong bonds with proteins, anion polysaccharides, forms chelate complexes with metals. It concentrates erythrocytes, blood coagulation factors and platelets at the bleeding site. Polymer carries charge which facilitates coagulation of blood in contact with erythrocytes and stimulates release of vasoconstrictors, such as thromboxane and endothelin [5].

Powder consisting of D-glucosamine and N-acetyl-D-glucosamine, for instance, Celox [8], can absorb blood 11 times its weight. Celox granules may be applied di-

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rectly on the wound and arrest bleeding without mechanical compression. Celox products are mainly used to stop bleeding in emergency cases. Bandages «Celox gauze», «Celox Rapid» are considered to be more effective than powder. Increase in hemostatic effectiveness was shown on an example of a combined impregnation of non-woven material with chitosan and PolySTAT polymer with clot-forming activity. In comparison of the obtained material with a commercially available gauze containing Celox Rapid chitosan, no noticeable differences in size of fibers, morphology and size of pores were seen. However, PolySTAT on chitosan basis demonstrated a more rapid absorption of blood [14].

A possibility to obtain derivatives analogous to cellulose derivatives, led to synthesis of chitin/chitosan esters. Composite hemostatic sponge was obtained from carboxymethyl chitosan and sodium alginate as the main materials with addition of $CaCl_2$ as a cross-linking agent [15]. On the contrary, N- и O-sulfated derivatives of carboxymethyl chitin/chitosan prevent blood coagulation due to selective adsorption and antithrombin.

*Amylopectin***.** Hemostasis with preparations of amylopectin (starch) is considered to be close to mechanical hemostasis. Amylopectin is formed by branched chains of α-glucose residues linked with glycoside bonds. Chains of amylopectin have more branches than amylase and less branches than glycogen; in general a macromolecule has a spherical shape. Amylopectin granules actively absorb a fluid fraction of blood, and hydration leads to irreversible alteration of structure – separation of chains and swelling of granules. Absorption of water from blood results in concentration of formed elements and of coagulation proteins. Starch (amylopectin) loses to hemostatic agents of gelatin and oxidized cellulose in terms of volume of absorbed fluid and resorption rate. Another disadvantage is a lower, in comparison with gelatin, speed of hemostasis.

Modern studies of starch are aimed at increase in the rapidity of swelling and in solubility. Polysaccharide hemostatic system PerClotR consists of particles of purified modified plant resorbable starch (AMPR). The study of 2009 demonstrated the effectiveness of hemostatic powder in the form of microporous polysaccharide «hemospheres» [16].

*Acrylic acid derivatives.* Acrylic acid is a simplest representative of monobasic unsaturated carbonic acids. Acrylic acid strongly irritates skin and mucosa of eyes (irritation threshold 0.04 mg/l). It possesses chemical properties of carbonic acids: forms salts, acid chloride, anhydrates, esters, amides, etc. In the presence of initiators of polymerization acrylic acid forms polyacrylic acid.

Polyacrylic acid interacts with albumin molecules by ionic bond mechanism with formation of a stable complex – matrix – and with further formation of a strong polymethacrylate film. This property is used for suturing the edges of wound using biological adhesive based on polyacrylate. With use of hydrophobic cyanoacrylate adhesive, hemostasis is realized via formation of an adhesive film on the wound surface. At the same time, cyanoacrylate adhesives are characterized by local and systemic toxicity and induce necrotic changes in the zone of application. Due to a rapid vitrification of such adhesives on the surface of wound and a weak bond with tissues, there are reported cases of early rejection of the adhesive plate with renewal of a threatening bleeding [17].

Feracryl is a partial iron salt of polyacrylic acid containing from 0.05 to 0.5% of iron. A unique hemostatic effect of feracryl is based on its ability to form polycomplexes with proteins in blood at pH from 2.9 to 4.0 even in the absence of fibrinogen.

Hemoblock is a silver salt of polyacrylic acid containing nanoparticles of silver which accounts for bactericidal and bacterios-

tatic effect of the drug. Hemoblock is applied externally in case of parenchymal and capillary bleedings. For this, sterile cotton and gauze bandages are soaked in Hemoblock and applied on the bleeding, preliminary dried surface. Hemostatic effect is achieved within 1-2 minutes through formation of a clot with blood plasma proteins, first of all, with albumin. Further on, albumin molecules reduce silver ions which provides the bactericidal effect of the film. Fibrin gradually replaces the superficial structure «hemoblock-protein», and polyacrylate matrix is plasmolyzed [18].

Polystat is a synthetic polymer on the basis of metacrylate and imitates F XIIIa-mediated stabilization of fibrin [19]. A prototype of PolySTAT is XIII blood coagulation factor – blood protein that strengthens a clot. PolySTAT induces hemostasis via cross-linking of fibrin matrix inside the clot. Besides, synthetic PolySTAT binds specially with fibrin monomers and uniformly integrates into fibrin fibers during fibrin polymerization which results in strengthening of hybrid polymer mesh with enhanced resistance to enzymatic degradation.

*Alumino silicate minerals* – zeolites (kaolin). Structural porosity of inorganic polymer $AlSiO_4$ defines application of aluminosilicates as adsorbents. Open scaffold-cavitary structure has a negative charge which enables it to hold back a high amount of cations, for instance, calcium – a cofactor in coagulation cascade. On the basis of synthetic zeolite, several effective LHA are developed. The preparations are insoluble, but biocompatible. In the US Army QuikClot preparation was adopted for stoppage of external massive bleedings. The hemostatic mechanism of QuikClot powder includes adsorption of water from blood, concentration of blood coagulation factors, activation of platelets and further implementation of coagulation cascade. Another preparation on the basis of zeolite – Hemostop – was developed in Russia. It is reasonable to pour the powder directly on the bleeding source and apply cotton tampon or bandage. Negative sides of zeolite include formation of burns due to emanation of heat in hydration and the necessity or manual compression within 5-7 minutes until sufficient soaking of the powder. To compensate for negative effects of zeolite it is partially hydrated (reduction of heating) and placed into a meshy carrier [20]. For instance, QuikClot Combat Gauze (QCG) – non-woven bandage impregnated with kaolin – was appreciated by medics because of its rolled shape that combines chemical and compression hemostasis [21].

So, analysis of scientific publications on the given topic shows a permanent attention to studying experience in application of a considerable quantity of hemostatic products for local arrest of bleeding, and also to new development in this field. It is worth to mention a wide range of LHA manufactured by specialized companies. With this, imported products are more variable in forms, but Russian manufacturers work to diversify the range of drugs within the same form.

Most effective are combined LHA. Accordingly, their activity is also based on combined mechanism. The majority of considered hemostatic components activate natural coagulation processes via concentration of coagulation factors, adhesion and aggregation of platelets. Adhesion and aggregation of coagulation factors on LHA based on collagen, gelatin, cellulose, chitin, starch is due to high hygroscopicity of these materials. Concentration of coagulation factors on kaolin is also due to a high absorbing capacity of this sorbent. Drying of the place of application, and increase in blood viscosity and in concentration of coagulation factors because of this, is a common principle of hemostatic activity of proteins, cellulous, alumino silicate materials, and other sorbents. Ability of polymers to create meshy structures and ability of kaolin to

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form ion complexes equally result in effective holding back of macromolecules and, accordingly, to increase in probability of clot formation.

Despite the existence of many various active components and the possibility of their use in different combinations, not a single hemostatic agent has been created so far, that could fully meet the demands of the modern medicine. A hemostatic agent should: stop bleeding (clot formation) within 2 minutes or faster; act in a wide temperature range; not damage the adjacent tissues; not cause painful sensations form compression or thermal damage; be ready for application and be easily used in extreme conditions; be suitable for use with complicated wounds; should degrade and be easily eliminated from the wound; have a long storage period; be bactericidal; be applicable in case of derangement of coagulation function; be economically efficient.

## Conclusion

At present, most effective trends in improvement of hemostatic agents are: synthesis of drugs on the basis of derivatives of chitosan or kaolin, creation of new forms (powders or granules, poured on the bleeding area, pastes, woven materials of special weaving; hemostatic agents carriers – powder applicators which may stop bleeding from deep wounds with a narrow input holes, and in cavities; Z-fold bandages (impregnated with the agent and fanfold); meshes holding kaolin; return to old and unfairly forgotten materials (cotton bandages); synthesis of new polymers, as for example, PolySTAT, synthesis of artificial platelets and other coagulation factors.

One more trend is creation of complex preparations combining sorption and clot-forming properties which include the majority of modern local hemostatic agents starting from hemostatic sponges manufactured by Zelyonaya Dubrava (Russia) and Nycomed, Takeda (Austria, Norway) and ending with hemostatic materials of MedTrade (Great Britain), Etiguette and Z-Medica (USA). Most effective are local hemostatic means on the basis of non-woven materials or sponges processed with a clot-forming substance. It is worth to mention a wide range of LHA manufactured by specialized companies. With this, imported products are more variable in physical forms of the basic material, while Russian manufacturers work to create more combinations of drugs on the basis of the same basic form.

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