Innovative technologies in extreme medicine

Local Hemostatic Agent (LHA) SX 77 «Spray tape»
The specifics of emergency medicine imposes special requirements upon the quality and timeliness of hemostasis. The presentation will show the characteristics of local hemostatic agents (LHA), i.e. drugs aimed at stopping bleedings. It will also envisage classification, the mechanisms of action, and the evidence of the effectiveness of the main types of hemostatic agents both of domestic and foreign production.

(see note*)

Special attention will be given to LHA clinically tested in emergency surgery and in the conditions of war.

Keywords of the presentation: SX-77, hemostasis, massive bleeding, disaster medicine, local hemostatic agents, emergency surgery.
The problem of massive bleedings is relevant with respect to all surgical specialties. A bleeding is a complication of many kinds of injuries and traumas. The biggest problem in this aspect is bleedings obtained as a result of injuries and traumas, which can result in death caused in the first place by the massive blood loss.
The classification of bleedings in injuries is based on the time of emergence thereof, location, and nature of the damaged blood vessels. Such classification can be pictured as follows (See Figure).
At present local hemostatic agents (LHA) are getting to be more and more widespread. The mode of action of LHA is targeted; they can be used in case large blood vessels are damaged and in cases of diffuse bleedings, when physical and systemic hemostasis techniques prove to be inefficient. Local hemostatic agents are widely used in surgical practice, and with the appearance of new drugs the scope of effective LHA use will increase replacing the traditional surgical manipulations when stopping a bleeding by the application procedure.
The Problem

Today the market offers a number of different types of dressing hemostatic materials, however, the use of some (collagen sponges, powders and chitosan bandages) in surgical practice and tactical medicine is limited due to their low hemostatic and antibacterial properties. The other drugs (for example, those based on fibrin, oxy and carboxymethylcellulose and zeolite) contribute to the inflammatory process, necrosis of parenchyma of organs and therefore development of infection due to their toxicity, invasiveness and antigenic properties, as well as local irritant effects. In the recent years, an extensive search has been in progress of a hemostatic drug that would provide a complex solution of different tasks arising in abundant bleedings.

- Strong Anticeptic Action
- Bioinert
- Hemostatic Properties
Today bleeding and blood loss is one of the principal causes of death of people wounded and injured in combat operations, disasters and accidents. In modern emergency surgery the problem of stopping bleedings in injuries, as well as in planned and emergency surgical interventions is still considered to be a complicated and underworked issue. The existing methods of stopping these types of bleedings (hemostatic sponges, powder and adhesive compositions, pharmacological methods of hemostasis, etc.) do not fully meet the requirements of modern tactical medicine. Some of the existing methods are often ineffective and highly traumatic, while others prove to be expensive.
The Solution

NEW APPLICABLE LOCAL HEMOSTATIC AGENT - «SX 77»

- Increased hemostatic ability
- Proven bactericidal properties
- Proven regenerative properties

The specified properties of SX-77 are achieved due to the special production technology.
The Product

With respect to the aggregate of its parameters, the new drug outperforms the local application drugs for bleeding wounds available in the market. When applied to a wound, SX-77 forms an "active hemostatic polymer bandage", whose integrated action solves the basic problems of the bleeding and its complications.
Advantages

**Action**
- High hemostatic effect
- Significant reduction of blood loss

**Base**
- Covering wounds of various depths and shapes
- Strong adhesion properties

**Composition**
- Strong antibactericidal properties
- Effective combat the wound infection
Medical assistance in emergency situations has its own specific features, which do not allow for certain methods of treatment and administration of certain drugs traditionally used in the clinical setting. This also applies to ways of stopping bleedings. For instance, the standard equipment of the operating rooms of the disaster medicine service field units does not include the complicated equipment for permanent hemostasis, such as plasma or ultrasonic coagulation.

Intra-operative bleeding during a surgery or immediately after it in the "field conditions" is one of the most dangerous complications in the surgical practice, which can shortly result in death.
The mechanism of action of SX-77 based on the principle "Applied andForgot" is its distinctive feature and makes it stand out among the other types of LHA.
Hemostasis is achieved through the use of various hemostatic drugs of local effect. There is a wide range of such hemostatic agents with a different active ingredient and mechanisms of handling the bleeding. Local hemostatic agents: the group of drugs originally used in the military medicine and eventually spread to the civil sector medicine. With the onset of the Iraq war, the attempts started aimed at finding, developing and implementing local hemostatic agents that could be used in field conditions both by the medics and soldiers themselves.

Several groups of such agents were developed differing by its mechanism of action, area of application and forms.
LHA Groups (see notes*)

1 group*
- **Patches and sponges from collagen/gelatine + thrombin**

2 group**
- **Patches and sponges from regenerated cellulose**
  (Surgicel, Gelitocel, Equcel, Blood Care Matrix)

3 group*** **Hemostatic glue**
- Fibrin и synthetic (SoSeal, Omnex, BioGlue, Glubron, Cardial)

4 group**** **powder LHA**
- Zeolite, chitosan (QuikClot, QuikClot ACS+, HemCon, Combat Gauze Celox)
While being effective when used in hospital, all of the above medications have proved to be of low effect in cases of heavy bleedings at the pre-hospital stage.
Unlike the drugs chosen for comparison, the locally developed SX-77 hemostatic is a carbonyl polymer complex, which contains various blood coagulation factors. When it enters in contact with the blood, a blood clot is formed which is tightly fixed to the wound surface. In addition, it accelerates regeneration and epithelization of the wound surface, facilitates the formation of granulation tissue, and provides an anti-edema and antiinflammatory effect.
**The properties of LHA «SX 77»**

- The hemostatic and antibacterial properties of this LHA, as well as its toxicity have been investigated in the course of pilot studies. It has been shown that it actively promotes clotting, and has strong adhesive and prolonged antibacterial properties; also it has proved to be well absorbed in tissues and have no side effects upon the body.
- It can be used as a local hemostatic agent for stopping intense diffuse bleedings in cases of the damaged parenchymal organs, as well as in wounds and open musculoskeletal injuries.
- The experimental studies conducted have shown that various samples of SX-77 are by far superior than the foreign and the domestic products included in the comparison group. SX-77 effectively shortens the clotting time in vitro, and proves to reduce the duration of bleeding and the amount of blood loss in the in vivo experiment; it possesses high biological inertness causing minimal tissue reaction when implanted. The drug developed on the basis of a hemostatic composition has very high hemostatic properties, which are combined with antibacterial activity.
SX-77 comes in the form of gel of various density. It should be noted that hemostasis can be easily achieved when the LHA is applied on the narrow deep wounds. Pilot application has demonstrated that the drug possesses a strong hemostatic effect regardless of the size, the area, and the profile of the bleeding wound.
The high hemostatic efficiency and the antiseptic activity are combined with high adhesive capacity and the optimal term of biodegradation. The optimal composition of the SX-77 components enable its tight application to the wound surface, thus providing for the mechanical stop of bleeding.
The phrase "tactical medicine" refers to providing pre-doctor first aid in emergency situations and in the battlefield.

SX-77 can be considered a tactical medicine remedy or a pre-doctor first aid tool used in certain procedures and algorithms of providing help in the battlefield. The current standards of providing pre-doctor first aid in the battlefield can be applied in the civilian segment alike.
SX-77 interacts with blood on the molecular level. When in contact with blood, the drug causes bonding and formation of a clot, which patches up the broken blood vessel. This makes it possible to use the hemostatic in order to stop bleedings in patients with clotting disorders and in hypothermia-stricken patients.
Field of Use:

- **Military medicine** • first aid at the stage of pre-hospital treatment
- **Disaster medicine** • medical aid at the stage of pre-hospital treatment
- **Surgical practice** • Stomatology, Traumatology • General surgery
The hemostatic remedy is able to quickly and effectively stop the strongest bleeding when providing first aid at the stage of pre-hospital treatment.

Today bleeding and blood loss is one of the principal causes of death of people wounded and injured in combat operations, disasters and accidents.

At present, the use of SX-77 is the best means for temporary hemostasis in cases of external bleedings. When in contact with blood, a gel-like blood clot is formed which stops bleeding. In addition, SX-77 has antibacterial properties, biocompatibility and ability of biodegradation (self dissolution).
The Russian innovative development based on a polymer matrix provides for the stop of external bleeding in any conditions and is irreplaceable in the battlefield.
The Speed of Bleeding Stop

LHA «SX 77» (10-50 seconds)

Other LHA (80-180 seconds)
Conclusions

- SX-77 has proved to reduce the duration of bleeding twice, and the amount of blood loss three-fold or more times compared to hemostatic remedies represented in the survey (collagen and gelatin sponges as well as foreign materials, such as Surgicel/Surgical Nu-Knit and chitosan powders), whose hemostatic activity is significantly inferior to that of the newly developed drug.

- SX-77 and materials based on it are characterized by high biological inertness, hemostatic and anti-inflammatory activity, which manifests itself in minimal reaction of the tissues adjacent to the wound surface. It effectively reduces the time of blood clotting, decreases the duration of bleeding and the amount of blood loss, and also reduces the severity of the septic process in the wound.

- Due to the convenient and easy-to-use gel form of the SX-77 hemostatic material, which possesses high antiseptic and antibacterial properties, it can be applied to wounds of different size and shape, without any fixation.
What is the Current Stage of the Development?

- Research and development activities have been completed; the technology has passed laboratory and pre-industrial tests.
- A pilot batch of the drug has been released.
- Activities aimed at obtaining the patent of the Russian Federation on the method of production are in progress.
- Qualitative physical and chemical analyses have been conducted.
- Technical specifications for the drug have been obtained.
- Pre-clinical trials of the drug have been conducted.
- A toxicological statement has been asked for.
- The certificate for a product intended for medical purposes is being prepared.
- Standard operating procedures with as to manufacturing of an LHA have been developed.
- Modern technological equipment meeting the technological requirements has been selected.
- Activities aimed at getting an international patent are in progress.
Many competitors have only one property...
... and only SX-77 combines all of these properties!

- The ability to stop bleedings, including those heavy;
- Antiseptic protection of the entire wound surface, regardless of the depth and the shape of the wound;
- Creating conditions for accelerated wound healing;
- High adhesion to the wound surface without removing the blood and exudate.
Conclusion

The fast and reliable stop of bleedings determines the success of the further progress in the treatment of injuries. In cases of bleedings having to do with discission or damage of major blood vessels, including veins, in mixed bleedings of medium/high intensity and in bleedings from parenchymal tissues, not all local hemostatic agents are capable of efficient hemostasis. In this regard, SX-77 proves to be the most effective drug. Highly efficient and easy to use, the drug can be used by medical staff, paramedic services, and the victims themselves in the course of providing self/reciprocal assistance in the conditions of combat and at the stage of medical evacuation in emergency situations. The drug should be used to stop massive external bleedings without the risk of repeated bleedings.
Thank you for your attention!
GROUP 1*

A large group of local hemostatic drugs is comprised by medications containing collagen and gelatin. These include different types of hemostatic collagen sponges, gelatine sponges and collagen patches. The hemostatic efficiency of the collagen-based LHA is determined by the action of the active components of hemostasis stimulation, which they contain. However, the disadvantage of the collagen-based LHA is their insufficient hemostatic effect and weak adhesion ability.

Gelatin can also be called a traditional LHA. Its mechanism of action is not fully clear. The most frequent explanation envisages the damage of platelets when in contact with gelatin and release of coagulation factors. Also, when the sponge form is used, the hygroscopic effect is deemed to take place. The main positive moment in the use of gelatin is the possibility of its complete degradation within 4-6 weeks. Gelatin is also effective in cases of capillary bleedings of the soft tissues. In its effectiveness it is comparable or even superior to collagen derivants. The efficiency of gelatin is enhanced when used in combination with other hemostatic agents.

Thrombin (bovine thrombin and recombinant human thrombin) can also be named among hemostatic agents used intraoperatively. The widely used combination of thrombin + gelatin effectively reduces blood loss after liver resection. It is often used in vascular surgeries. The effectiveness of this very combination reduces the amount of blood loss and the volume of blood transfusion.

Both kinds of thrombin have a high hemostatic effect, though bovine thrombin causes a high immune response and production of antibodies. Also, drugs with human thrombin are quite expensive. These factors limit their wide use.
GROUP 2**

- Oxidized regenerated cellulose (Surgicel, Gelitocel, Equcel, Blood Care Matrix) is widely used as a hemostatic agent. The mechanisms of its action are quite diverse. It adsorbs and commits itself to coagulation factors and platelets; due to the low PH of cellulose, it results in vasoconstriction in the place where it is applied. Most often it is used in the form of tissue patches. This is a more convenient form, because compared to a sponge, it is softer and can be applied to a wound of any configuration. It completely degrades within 1-3 weeks. However, due to the risk of granulomas in the area, many guidelines suggest that it should be removed after hemostasis is achieved.

- The disadvantages of drugs of this group are the short duration of action, its low specific activity, and the potential probability of the wound infection in field conditions. As well, its disadvantages include the high price of drugs made from regenerated cellulose and its limited hemostatic activity in cases of massive bleedings.
GROUP 3

- Fibrin glues: The hemostatic mechanism is the formation of a fibrin clot at the site of application. In order to achieve hemostasis and extend it, fibrin glues are combined with antifibrinolytic drugs: tranexamic acid and aprotinin. For fibrin glue it is possible to control the speed of fibrin clot formation by using different concentrations of thrombin in this mixture.

- Synthetic glues provide mechanical sealing of vessels (defects of those). These are cyanoacrylate adhesives and polymers of polyethylene glycol (SoSeal, Omnex, BioGlue, Glubron, Cardial). A distinctive feature of use of this type of hemostatic agents is the possibility to apply them only upon preliminarily dried wound surfaces.
GROUP 4**** (modern sponge and powder LHA)

Developed in the United States, QuikClot was designed to stop massive external bleedings, and has been used in combat situations. QuikClot is a granular zeolite which quickly absorbs water emitting a large amount of heat. The heating of the surrounding soft tissues to 70-95°C can cause thermal burns, which is one of the main disadvantages of this remedy. Not long ago a modification of QuikClot was created in which this shortcoming is partially resolved.

In the United States Army HemCon hemostatic drug (deacetylated chitosan placed on a sterile foam pad) is on the list of supply items. When in contact with negatively charged erythrocytes, the salt of chitosan quickly enters into cross-connection, firmly adhering blood elements on the surface of the wound. This explains the major hemostatic effect of HemCon, which does not cause a thermal reaction. Celox, also a mucoadhesive LHA, is based on chitosan as well. It comes in granules or in the form of chitosan impregnated wrapped gauze (Celox Gauze). Celox is a highly powerful hemostatic, it can absorb moisture in the volume exceeding its own mass 11 times.

Currently the following LHA are on list of supply items in the United States Army and the armies of NATO countries: QuikClot, QuikClot ACS +, HemSon, Combat Celox Gauze.

Today such drugs in the form of powder and nonwoven materials are manufactured by the British MedTrade Products Ltd. and the American HemCon Medical Technologies Inc. companies respectively.
The most widespread foreign manufactured hemostatic in our country is Tachocomb (of Nycomed), which is a collagen patch, one of whose sides is coated with highly concentrated thrombin, fibrinogen and aprotinin. After the contact with a bleeding wound or other fluids, blood clotting factors are dissolved and connections are formed between the collagen carrier and the wound surface. At the same time Tachocomb has a weak ability with respect to sealing of the wound surface, which is very necessary in some situations.
**Disadvantages of the existing LHA**

- The listed powder LHA adhere the **blood elements** on the surface of the wound, however they have weak adhesive properties with respect to the entire surface of the wound, which makes it impossible to stop the heavy bleeding without additional mechanical tamponade and exclude the likelihood of repeated heavy bleedings. As well, the disadvantages of LHA of this group include very weak antibacterial properties of their main active components. The use of LHA of this group in the field conditions often leads to septic complications.

- As can be seen from the above, all of the listed drugs have their individual characteristics, both advantages and disadvantages. Not all of them combine the effective blood clotting action with a well pronounced adhesive ability; in addition, some of them are easily soluble in water. As a result, in cases of strong bleedings these drugs happen to be washed off the bleeding surface failing to provide the hemostatic action.

- Most of the drugs are manufactured in the form of sponges, film, gauze and other similar forms, which in comparison with the powder form provide for a limited surface of the direct contact with the blood; thus, the speed and efficiency of the impact upon the blood coagulating system is limited in the first groups of the drugs listed below. As for powder hemostatic drugs, they prove to be difficult to work with in extreme conditions: the powder gets blown off by the wind, gets spilled or contaminated.