Mechanism of action of topical hemostatic and adhesive tissue agents

Mecanismo de ação dos agentes hemostáticos locais e adesivos tissulares

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ABSTRACT

A wide variety of topical hemostatic agents, sealants, and tissue adhesives is currently available. Knowledge of the mechanism of action of each of them is essential for choosing the ideal agent for each type of hemorrhage. Hemostatic agents are divided into two groups according to mechanism of action: a) active, which activates platelets b) passive or mechanical, which promotes blood absorption, increase in volume, and creates pressure on the site of the bleeding. Active agents can be used in coagulopathies and use human plasma components like thrombin and fibrin. As such, they can transmit viral diseases and are more expensive. Mechanical agents, because they stop the bleeding due to volume increase cannot be used in confined areas. This article considers the characteristics of various hemostatic agents.

Key words: Hemostatics; Tissue Adhesive; General Surgery.

INTRODUCTION

Proper control of bleeding during surgery is paramount to good per and postoperative evolution. Despite the significant advances in surgical techniques, excessive bleeding remains a problem and is the most serious complication associated with surgical procedures.¹ Excessive bleeding is related to patients characteristics, iatrogenic phenomena, and specific procedures.¹ Patient-related variables are abnormalities in blood coagulation, use of anticoagulants, and other diseases, such as diabetes mellitus, systemic arterial hypertension and renal failure. Eventual iatrogenic phenom-
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Reactions called “coagulation cascade”. The coagulation factors that play a major role in this cascade are X and V and thrombin. Factor V has a crucial role since it makes the extrinsic and intrinsic pathways of coagulation converge and has prime importance in the formation of thrombin, which is the final protein of the coagulation cascade, responsible for creating fibrin.

MECHANISM OF ACTION OF LOCAL HEMOSTATIC AGENTS

Local hemostatic agents act in two ways, namely:

a. active hemostatics: promote platelet activation and activation in the final step of coagulation;

b. passive or mechanical hemostatics act in order to increase volume (they swell) by absorbing blood, which creates pressure on the site of bleeding. They also act through contact with platelets, which creates the foundation that promotes platelet aggregation. Active hemostatic agents include thrombin and the products in which thrombin is associated with passive hemostatic agents and fibrin sealant, while passive hemostatic agents include collagen preparations, gelatin, cellulose and polysaccharides. Active hemostatic agents can be used in association with passive ones (Figure 1, Table 1).

METHODS

The research was conducted on the PubMed database (www.ncbi.nlm.nih.gov/pubmed/) and Google (www.google.com), using the descriptors “topic hemostatic agents, sealants, and tissue adhesives”. Many studies were found, but the majority did not refer to the mechanisms of action of local hemostatic agents, sealants, and tissue adhesives. Studies selected for this review were chosen after titles and abstracts resulting from this search were read. Other works included were pertinent to the subject and were found in the references cited in the selected works.

BLOOD COAGULATION

Blood coagulation is a process that requires coordinated activity of the platelets and coagulation factors for the formation of stable platelets and fibrin clots. Coagulation occurs in primary and secondary pathways. The primary pathway occurs through release of platelets’ vasoactive and activating factors in response to injury of the tissue’s blood vessels, such as tissue VIIa, IX and X factors. These substances cause temporary vasoconstriction and platelet adhesion to the site of the injury to form a soft plug. In the secondary hemostasis, the activated platelets secrete serotonin, prostaglandin and tromboxane to maintain local vasoconstriction while the coagulation cascade is activated through the release of injured tissue factors resulting in the formation of fibrin and in cross-link and stabilization of the platelet plug.

Coagulation factors are produced in the liver, circulate with the blood inside the vessels and, when these vessels are injured, participate in sequential enzymatic
Collagen

Collagen, when in contact with the bleeding surface, attracts platelets which adhere to the collagen fibrils, thus promoting degranulation and initiating platelet aggregation that results in thrombi formation in the collagen interstices and initiates formation of the physiological platelet plug. Microfibrillar collagen is made out of bovine collagen and processed into microcrystals, which can be manipulated to be offered as hemostatic agents as powder, tissues, and foam.

Cellulose

Oxidized and regenerated cellulose is a local bioabsorbable hemostatic agent similar to gauze. Cellulose-based products are easy to handle and do not adhere to surgical instruments, unlike collagen-based products. Nevertheless, these products are not biodegradable and should only be used in small amounts.

Gelatin

The characteristics of gelatin allow products that contain it to be used in wounds with irregular contours, which allows them to acquire the contours and geometry of the wound, thereby enlarging and adapting to the wound’s format, promoting a mechanical tamponade effect. Thus, the swelling of the gelatin hemostatic agent restrains blood flow and promote a stable matrix around which the clot will form.
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Polysaccharides

Polysaccharides (Arista AH) are derived from plants and act by blood dehydration. They act as a sieve causing the blood’s solid components to concentrate, increasing the formation of a barrier for the bleeding, and assisting when the activity of platelets and coagulation proteins is normal. Polysaccharides can swell up to 500%. For this reason, this material is not safe in neurological, urological and ophthalmological operations.

Sealants and tissue adhesives

Thrombin Sealant

Thrombin is a natural enzyme with an important role in hemostasis and inflammation. It is derived from prothrombin as a result of the extrinsic and intrinsic pathways of coagulation, and is the foundation for the fibrin clot as it turns fibrinogen into fibrin. Thrombin derived from bovine serum has proved to be very effective, with a strong power to convert fibrinogen into fibrin, to activate platelets and to induce vasoconstriction. However, it has caused immunological reactions. Thrombin derived from human plasma has the potential risk of viral disease transmission. For this reason, recombinant thrombin was prepared, but its cost is high. Thrombin compounds are also available with gelatin and collagen.

Polyethylene glycol polymers

Refers to synthetic local hemostatic agents formed by hydrogels that promote organic tissue sealing. When applied to the wound, the product absorbs the fluids and expands, closing the injury and creating pressure on the tissues, thus ceasing the bleeding. The product consists of two polymeric solutions of ethylene glycol and hydrogen chloride and sodium phosphate and sodium carbonate solution. This hemostatic agent is indicated as an adjunct to hemostasis of blood vessels for mechanical sealing of leakage areas or to diminish or prevent air leakage in lung operations.

Cyanoacrylate adhesive

Cyanoacrylate acts by polymerization when in contact with organic proteins that act as catalysts and this reaction produces heat and forms a crust on the surface where applied. This adhesive does not depend on the state of blood coagulation and can be used when there is coagulopathy. Its power is identical to that of sutures in keeping the tissues together. Cyanoacrylate is bactericidal and bacteriostatic, and in its new formula, the cyanoacrylate glue has minimal tissue toxicity.

CONCLUSIONS

There are many local hemostatic agents, tissue sealants, and adhesives currently available (Table 2). The choice for the most suitable agent for a spe-
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A specific kind of bleeding depends on the knowledge of their mechanism of action. The use of gelatin should be avoided around nerves and in confined areas because it uses volume increase to create a mechanical barrier to bleeding. Thrombin combined with oxidized cellulose, however, can be used in these circumstances. Collagen, gelatin and cellulose have little or no effect in patients using heparin or anti-platelet drugs. In contrast, hemostatic agents based on thrombin or fibrin, because they work in the final stages of coagulation, are indicated if these medicines are used and in case of clotting disorders. It is important to consider that no single hemostatic agent can be effective in all cases of bleeding.

**Table 2 - Product, brand name, manufacturer, and mechanism of action**

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celullose</td>
<td>Surgic</td>
<td>Johnson&amp;Johnson</td>
<td>Contact activation with start of coagulation cascade</td>
</tr>
<tr>
<td>Collagen</td>
<td>Avitene/Instat/</td>
<td>Bard/Johnson&amp;Johnson/</td>
<td>Contact activation with start of coagulation cascade and promotion of platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>Lyosytpt</td>
<td>Braun</td>
<td></td>
</tr>
<tr>
<td>Gelatin</td>
<td>Gelfoan/Surgiflo</td>
<td>Upjohn/Johnson&amp;Johnson</td>
<td>Contact activation with start of coagulation cascade</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>Arista HA</td>
<td>Medafor</td>
<td>Act by dehydrating the blood to concentrate the blood’s solid elements and promote barrier formation</td>
</tr>
<tr>
<td>Thrombin</td>
<td>Evithrom/Recothrom</td>
<td>Johnson&amp;Johnson/ZymeGenetics</td>
<td>Interacts with fibrinogen in the blood and forms the fibrin clot</td>
</tr>
<tr>
<td>Thrombin + gelatin</td>
<td>FloSeal</td>
<td>Baxter</td>
<td>Hemostatic fluid which, when applied to tissues, causes polymerization and hardens. When the material comes into contact with the blood, it begins to join in areas where there is fibrinogen</td>
</tr>
<tr>
<td>Thrombin + collagen</td>
<td>TachoSil</td>
<td>Baxter</td>
<td>The product is a dry sponge, which can be used in places with active bleeding and acts by releasing coagulation factors</td>
</tr>
<tr>
<td>Fibrin Adhesive</td>
<td>Tissucol/Beriplast/</td>
<td>Baxter/Aventis/Johnson&amp;Johnson</td>
<td>Two separate syringes provide fibrinogen, thrombin and factor XIII which, blended, form the clot</td>
</tr>
<tr>
<td>Albumin + Glutaraldehyde</td>
<td>Bioglu</td>
<td>Cryolife</td>
<td>Albumin and glutaraldehyde are cross-linked with tissue proteins to form a strong adhesive</td>
</tr>
<tr>
<td>Ethylene-glycol polymers</td>
<td>CoSeal/DuraSeal</td>
<td>Baxter/Covidien</td>
<td>Ethylene-glycol polymers absorb large amounts of fluid and expand, closing the wound and creating pressure against the bleeding site</td>
</tr>
<tr>
<td>Cyanoacrylate adhesive</td>
<td>Glubran/0mnex</td>
<td>Gem/Johnson&amp;Johnson</td>
<td>The liquid cyanoacrylate monomers form polymers in the presence of water and quickly paste adjacent surfaces</td>
</tr>
</tbody>
</table>

**REFERENCES**

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