REVIEW ARTICLE

Mechanism of action of topical hemostatic and adhesive tissue agents

Mecanismo de ação dos agentes hemostáticos locais e adesivos tissulares

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DOI: 10.5935/2238-3182.20130077

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.

RESUMO

Existe disponível, atualmente, grande variedade de agentes hemostáticos locais, vedantes e adesivos tissulares. O conhecimento do mecanismo de ação de cada um deles é primordial para a escolha do agente ideal para cada tipo de hemorragia. Os agentes hemostáticos são divididos em dois grupos, de acordo com seus mecanismos de ação: a) ativos - os ativadores das plaquetas; b) passivos ou mecânicos - promotores da absorção do sangue, aumentando o seu volume e pressionando o local do sangramento. Os agentes ativos podem ser usados nas coagulopatias, utilizam componentes do plasma humano como trombina e fibrina e, por isto, podem transmitir doenças virais e são mais dispendiosos. Os agentes mecânicos, por criarem uma barreira ao sangramento devido ao aumento de volume, não podem ser usados em áreas confinadas. Neste artigo são feitas considerações sobre as características dos vários agentes hemostáticos.

***Palavras-chave:** Hemostáticos; Adesivos Teciduais; Cirurgia Geral.*

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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-

Submitted: 08/01/2011
Approved: 11/23/2011

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ena include hypothermia, hemodilution, metabolic acidosis, and inadequate surgical technique. Surgeries involving the spinal cord, as well as heart surgeries with the use of extracorporeal circulation due to high doses of heparin and to hemodilution cause excessive bleeding, and so do procedures in highly vascularized areas. Comparable situations include those that require an approach on friable tissues, reoperations in large areas with adhesion and bleeding on bone surfaces.[2] When faced with these situations, local hemostatics, sealants, and tissue adhesives are alternatives to prevent excessive bleeding.

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[2-4] 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 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;[2,5]
b. passive or mechanical hemostatics:[2,5] 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).

There is a third category of hemostatic agents that includes tissue adhesives and sealants made up of fibrin sealant, ethylene glycol hydrogels, albumin glue with glutaraldehyde and cyanoacrylate, which, when applied onto the site of the bleeding, favor hemostasis by tissue adhesion.[1,5,6] Tissue sealants and adhesives are particularly suitable in cases of arterial bleeding and vascular sutures.

Active hemostatic agents

The basic mechanism of action of these agents is to provide a physical structure around the site of the bleeding in which platelets can aggregate, allowing clot to formed. Thrombin has been used to stimulate platelet aggregation and convert fibrinogen into fibrin in the site of the bleeding. Thrombin can be applied as a powder, spray or solution, and is indicated in localized refractory bleeding and in other measures during neurological, orthopedic, cardiac, and vascular prodedures.[1]

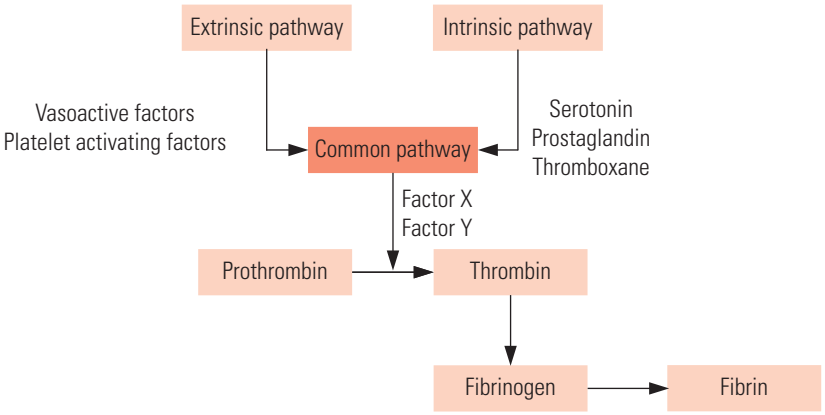

Figure 1 - Simplified scheme of the coagulation cascade.

Table 1 - Products grouped in local hemostatic agents, tissue sealants and adhesives

Agents	Available substances
Passive	Cellulose, collagen, gelatin, polysaccharides
Active	Thrombin, thrombin + gelatin, thrombin + collagen
Sealants and Adhesives	Fibrin adhesive, albumin + glutaraldehyde, ethylene-glycol polymers, cyanoacrylate adhesive

Thrombin was initially made of bovine thrombin but is currently available as recombinant human thrombin, developed to reduce the risk of communicable diseases potentially transmitted by human thrombin and to avoid the immune reactions of bovine thrombin.[1] However, these modifications sharply raise the price of the product. Thrombin can be more easily applied in combination with passive hemostatic agents, such as gelatin sponges soaked in thrombin.[7]

Passive or mechanical hemostatic agents

The basic mechanism of action of mechanical hemostatic agents is to provide a foundation upon which the platelets can aggregate and form a clot hence creating a mechanical barrier to stop the bleeding. Mechanical hemostatic agents are available in various forms and methods of application and these are important factors to determine their efficacy.[7] The sponge and wool forms are the most commonly used among surgeons, although wool (microfibrilar) and powder can have electrostatic charge and cause these products to adhere to the surgical instruments and gloves, making them more difficult to handle.[2]

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.[7,8] 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.[9]

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.[5,7,8]

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.[2,7,8]

Polysaccharides

Polysaccharides (Arista AH) are derived from plants and act by blodd 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%.[5] For this reason, this material is not safe in neurological, urological and ophthalmological operations.[5,8]

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.[10] 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.[8,11] Thrombin compounds are also available with gelatin and collagen.[8,11,12]

Fibrin sealant

Fibrin sealant is prepared in two syringes, one with fibrinogen concentrate, factor XIII and fibronectin, and the other one with thrombin and tranexamic acid or aprotinin.[13] The components of the two syringes are mixed at the time of application. The addition of aprotinin or tranexamic acid contributes to stabilizing the fibrin clot. Fibrinogen is the precursor of fibrin, which represents the basic element of the clot. The transformation of fibrinogen into stable fibrin takes place through the action of thrombin and the factor XIII. The fibrin sealant mimics the final steps of the coagulation cascade autonomously in relation to the mechanism of coagulation. It is also effective in patients with clotting disorders or for patients receiving heparin or anticoagulants.[13,14]

Bovine albumin and glutaraldehyde

The albumin-glutaraldehyde glue also consists of two separate solutions that are dispensed by a dual-chamber syringe system. The solutions are mixed inside the applicator at the time of its use and the cross-links begin. Glutaraldehyde's covalent molecules connect with the albumin molecules and, when applied, also bind to the proteins of the local bleeding, creating a mechanical seal independent from the body's mechanism of coagulation.[14,15] This adhesive is resistant, easy to use, and is more affordable than most. The use of the albumin-glutaraldehyde glue, however, can be associated with tissue injury, embolism and pseudoaneurysm.[16]

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[5,17,18] or to diminish or prevent air leakage in lung operations.[19]

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.[20] Its power is identical to that of sutures in keeping the tissues together.[21] Cyanoacrylate is bactericidal and bacteriostatic, and in its new formula, the cyanoacrylate glue has minimal tissue toxicity.[22]

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-

cific 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 antiplatelet 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

Product	Brand name	Manufacturer	Mechanism of action
Celullose	Surgicel	Johnson&Johnson	Contact activation with start of coagulation cascade
Collagen	Avitene/Instat/ Lyostypt	Bard/ Johnson&Johnson/ Braun	Contact activation with start of coagulation cascade and promotion of platelet aggregation
Gelatin	Gelfoan/Surgiflo	Upjohn/ Johnson&Johnson	Contact activation with start of coagulation cascade
Polysaccharides	Arista HA	Medafor	Act by dehydrating the blood to concentrate the blood's solid elements and promote barrier formation
Thrombin	Evithrom/Recothrom	Johnson&Johnson/ ZymoGenetics	Interacts with fibrinogen in the blood and forms the fibrin clot
Thrombin + gelatin	FloSeal	Baxter	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
Thrombin + collagen	TachoSil	Baxter	The product is a dry sponge, which can be used in places with active bleeding and acts by releasing coagulation factors
Fibrin Adhesive	Tissucol/Beriplast/ Quixil	Baxter/Aventis/ Johnson&Johnson	Two separate syringes provide fibrinogen, thrombin and factor XIII which, blended, form the clot
Albumin + Glutaral-dehyde	Bioglue	Cryolife	Albumin and glutaraldehyde are cross-linked with tissue proteins to form a strong adhesive
Ethylene-glycol polymers	CoSeal/DuraSeal	Baxter/Covidien	Ethylene-glycol polymers absorb large amounts of fluid and expand, closing the wound and creating pressure against the bleeding site
Cyanoacrylate adhesive	Glubran/Omnex	Gem/Johnson&Johnson	The liquid cyanoacrylate monomers form polymers in the presence of water and quickly paste adjacent surfaces

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