Brazilian Journal of Anesthesiology 2021;71(1) 65–75

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

NARRATIVE REVIEW

Perioperative hyperfibrinolysis – physiology and pathophysiology

David Silveira Marinho [a,b,*]

[a] *Hospital Geral de Fortaleza, Serviço de Anestesiologia, Unidade de Transplante Hepático, Fortaleza, CE, Brazil*
[b] *Instituto Dr. José Frota, Serviço de Anestesiologia, Membro do Comitê Transfusional, Fortaleza, CE, Brazil*

Received 22 March 2019; accepted 17 May 2020
Available online 25 December 2020

KEYWORDS
Hemostasis;
Fibrinolysis;
Blood clotting disorders

Abstract
Introduction and objectives: The role of the anesthesiologist in the perioperative management of hemostasis has attracted increasing attention. The fibrinolytic system participates in hemostasis, removing clots after repair of the vascular injury. Over the past two decades, several studies have assessed the efficacy and safety of antifibrinolytic agents in reducing perioperative bleeding and transfusion requirements. Some of the conditions that seem to benefit from antifibrinolytic drugs involve trauma, postpartum hemorrhage, cardiac surgery, spine surgery, knee or hip arthroplasty, urological and gynecological surgery, among others. However, there are currently few publications focusing on the perioperative features of fibrinolytic system, which will be the subject of the present review.
Content and conclusions: Fibrinolytic physiology, its relationship with the clot structure and its perioperative behavior are described. Pathophysiological mechanisms related to anesthesiology clinical practice and their possible perioperative scenarios are addressed according to a suggested classification. This article aims to provide anesthesiologists with a broader understanding of the normal functioning of fibrinolysis, the mechanisms of possible deviations from normality in the perioperative period, the pathophysiological rationale supporting the current indications of antifibrinolytics, and some recent outcomes obtained with their use.

* Corresponding author.
E-mail: davidsmarinho@gmail.com

https://doi.org/10.1016/j.bjane.2020.12.007

Introduction

For a better understanding of the physiological events of hemostasis, we can group them into three systems: the primary hemostatic system, the secondary hemostatic system, and the fibrinolytic system. Hemostasis requires mechanisms both to stop bleeding by the hemostatic plug formation (coagulation) and also to restrain and dissolve the plug after vascular injury repair, so that blood circulation through the vessel is reestablished (fibrinolysis). In a functional and dynamic balance, these two processes have their activities finely integrated and adjusted to each other, and, within each process, there is a complex and delicate balance between enzymes and inhibitory proteins. Controlled mostly by the endothelium, this fine regulation tries not to compromise initial stability of the clot, and to restrict the action of these mechanisms to the injured area. Usually, the fibrinolytic system remains dormant. However, its activity can be influenced by physiological or pathological events,[1] and fibrinolytic system imbalances can generate abnormal hemostatic phenotypes ranging from thrombosis (hypofibrinolysis) to bleeding (hyperfibrinolysis).

Over the past two decades, clinical trials and reviews with meta-analyses have tried answering the question ''Which scenarios have shown improved outcomes and safety after administration of antifibrinolytics?''. Conversely, although it seems reasonable trying to carefully understand a disease before evaluating its treatment, there are very few publications on the perioperative features of the fibrinolytic system. Consequently, questions such as ''What mechanisms support the use of antifibrinolytics?'' or ''Why should we use them in this scenario?'' still require attention. Thus, the present article aims to provide anesthesiologists with a comprehensive understanding of the normal functioning of fibrinolysis, the mechanisms of perioperative deviations from normality, the pathophysiological rationale supporting the use of antifibrinolytics, and some recent outcomes obtained with their administration.

Physiological mechanisms

Fibrinolytic activity

Plasmin is the key enzyme for the fibrin degradation mechanism. It is released by the liver as a zymogen – called plasminogen – whose activators and inhibitors regulate fibrinolytic activity.

There are three plasminogen activators: Tissue Plasminogen Activator (t-PA), Urokinase-type Plasminogen Activator (u-PA), in addition to fibrinolytic activation through the intrinsic coagulation pathway. Tissue plasminogen activator is the main agent involved in the dissolution of fibrin in the circulation and is synthesized and secreted by endothelial cells. Urokinase plasminogen activator is produced by monocytes, macrophages, and the urinary epithelium. Although the activity of u-PA has some relevance for local hyperfibrinolysis in tissues of the genitourinary tract,[2] its action only is enhanced when u-PA binds to a specific receptor on the cell surface. For this reason, it is believed that the greatest importance of this activator lies in the pericellular proteolysis required for cell migration and healing. Finally, the intrinsic coagulation pathway directly activates plasminogen or favors its activation via t-PA and u-PA, what may be important in scenarios where blood is exposed to non-endothelial surfaces (which activate the intrinsic pathway), as on Extracorporeal Circulation Circuits (ECC)[3] and on hemodialysis.[4] Due to its leading physiological role, this discussion will focus on the activation of plasminogen by t-PA (Fig. 1).

Once endothelial integrity is broken, the reactions of the coagulation system are triggered, which result in thrombin production and subsequent fibrinogen polymerization into fibrin. Endothelial damage also prompts secretion of t-PA by the injured endothelial cells. Such secretion is enhanced by the presence of thrombin, histamine, bradykinin, hypoxia and by an increase in adrenergic tonus, which are often present in situations of endothelial damage. Dispersed through the plasma permeating the fibrin mesh in formation, there are several molecules of plasminogen and t-PA secreted by the endothelium. Conformational

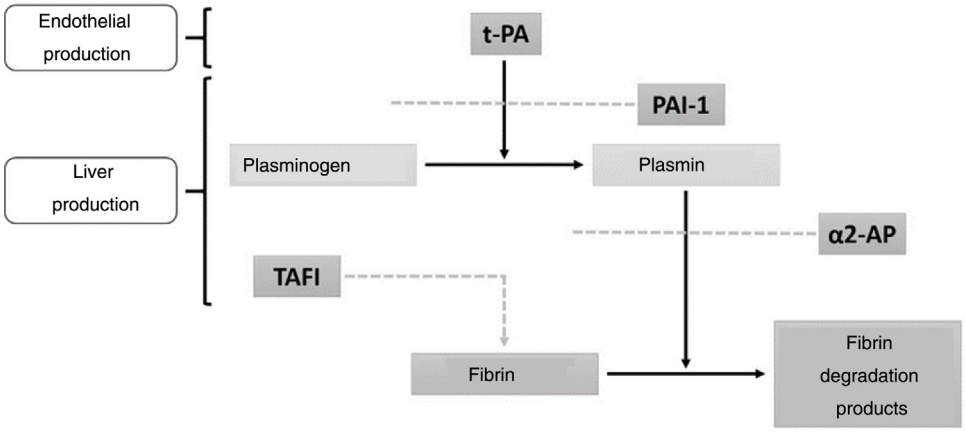

Figure 1 Physiological activators and inhibitors of fibrinolysis. Tissue plasminogen activator (t-PA); Plasminogen Activator Inhibitor 1 (PAI-1); α2-antiplasmin (α2-AP); Thrombin-activatable Fibrinolysis Inhibitor (TAFI).

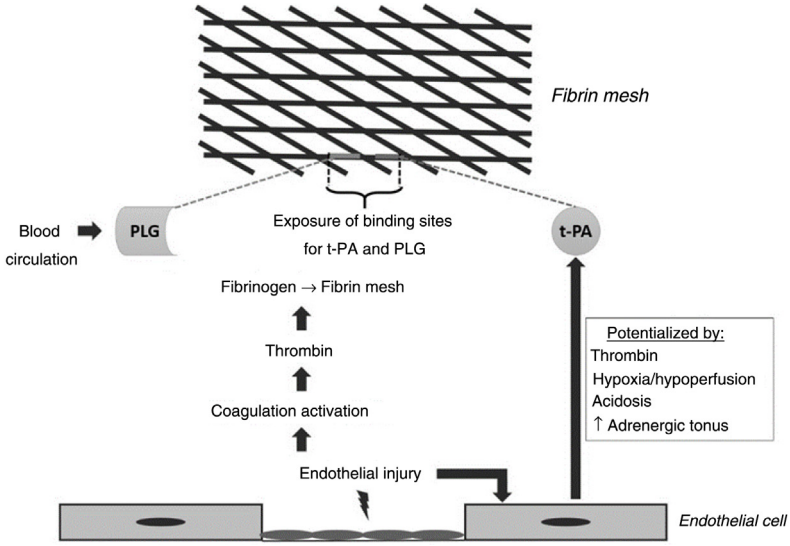

Figure 2 Early events of coagulation and fibrinolysis. Plasminogen (PLG); Tissue plasminogen activator (t-PA).

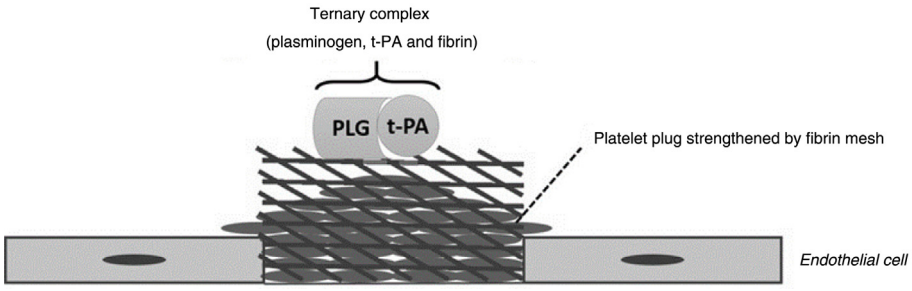

Figure 3 Formation of a ternary complex between plasminogen, t-PA and fibrin.

changes that occur during fibrin polymerization induce exposure of sites (previously hidden inside the 3-D structure of fibrinogen) for the binding of plasminogen and t-PA (Fig. 2).

As binding sites are exposed, plasminogen binds to lysine amino acids on the fibrinogen structure; in its turn, t-PA binding sites are spatially close to those of plasminogen. The primary binding sites of t-PA do not involve lysine residues, but this amino acid appears to have some role in stabilizing the binding of this activator on the fibrin mesh.[5]

Therefore, only after fibrin formation, binding sites are exposed for the formation of a ternary complex involving plasminogen, t-PA and fibrin (Fig. 3). The spatial positioning of t-PA in this complex enables it to cleave a plasminogen peptide bond, converting it to plasmin. In the absence of fibrin, t-PA is a poor plasminogen activator, so that only a small fraction of plasmin is activated freely in the circulation. However, the activation rate of plasminogen by t-PA increases circa 1,000 times when these two molecules are aligned on the fibrin surface.

After being activated, plasmin remains bound to its initial binding site, but starts to cleave several lysine or arginine peptide bonds in regions close to it or in nearby fibrin strands. As it cleaves a bond between a lysine (or arginine) and another amino acid, plasmin induces the exposure of a lysine (or arginine) residue at one of the ends of the cleaved bond. Such exposed residue works as a new binding site for other plasminogen molecules that are close to the fibrin mesh. Thus, the exposure of this c̈racked areaön fibrin mesh provides plasminogen access to multiple binding sites, working as a positive feedback, and exponentially increasing the rate of fibrinolysis[6] (Fig. 4).

Plasmin is a serine protease with broad substrate specificity. In addition to its major action on fibrin mesh, in conditions presenting systemic hyperplasminemia (described later), plasmin is also capable of cleaving and inactivating coagulation factors V and VIII and some platelet glycoproteins, which expands the range of deleterious actions of plasmin on coagulation.

While plasmin and t-PA stay bound to lysine residues on the fibrin surface, they are relatively protected from the action of endogenous inhibitors or antifibrinolytic drugs, given that the binding sites of these pro-fibrinolytic molecules are occupied by that amino acid. However, after breaking multiple lysine (or arginine) bonds nearby, plasmin and t-PA molecules release themselves from the fibrin mesh and then are rapidly inactivated by their inhibitors (Fig. 5).

The main endogenous inhibitors of fibrinolysis are Thrombin-Activatable Fibrinolysis Inhibitor (TAFI), Plasminogen Activator Inhibitor 1 (PAI-1), and alpha-2-Antiplasmin (α2-AP). PAI-1 and α2-AP are enzymes of the group of serpins. Serpins act as ''suicide inhibitors'' that form 1:1

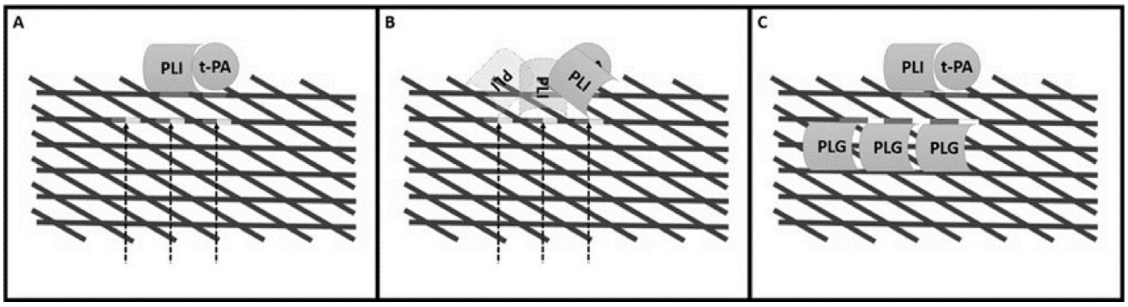

Figure 4 Dynamic action of t-PA and plasmin on fibrin mesh. A: Arrows indicate peptide bonds (formed by lysine and another amino acid) close to the plasmin molecule; B: Cleavage of several peptide bonds by a single plasmin molecule; C: Lysine residues originated from the cleaved peptide bond become exposed and offer a new binding site for several other plasminogen molecules, starting a positive feedback. Plasminogen (PLG); Plasmin (PLI); Tissue plasminogen activator (t-PA).

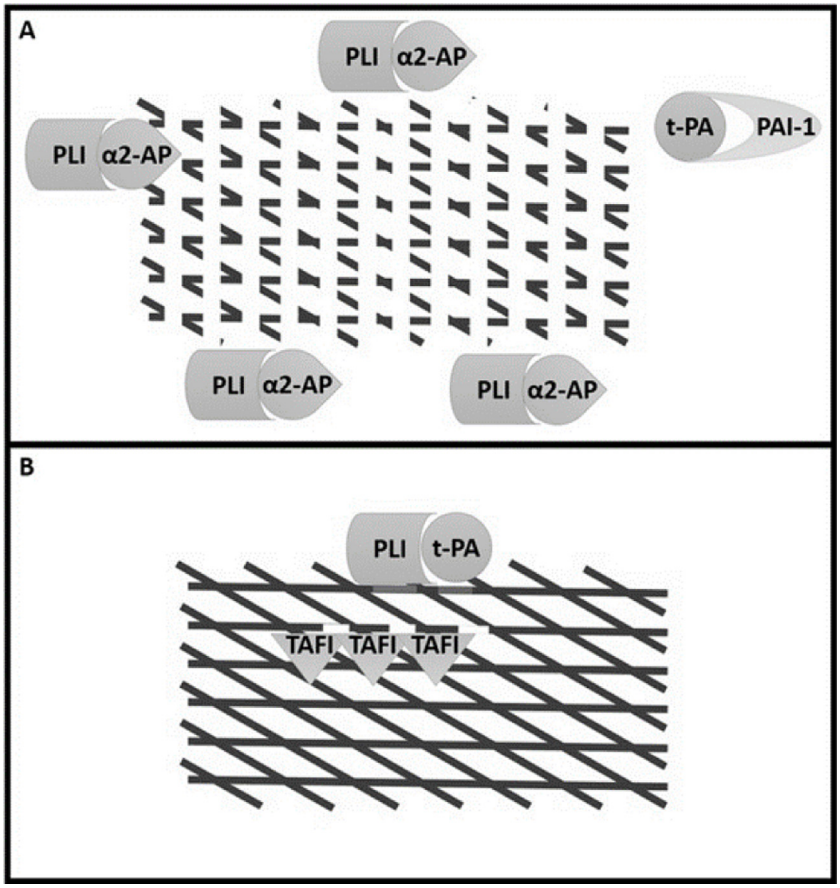

Figure 5 Control of fibrinolysis by inhibitors' action after detachment of t-PA and plasmin from the fibrin mesh surface. A: After completing the fibrin mesh breakdown, plasmin and t-PA are released into the surrounding plasma, where they are captured by their inhibitors (α2-AP and PAI-1, respectively). B: Although it does not restore the fibrin fragmented points, TAFI removes the newly exposed lysine residues, preventing additional plasminogen molecules from binding and intensifying fibrinolysis and blocking the positive feedback described previously. Plasmin (PLI); Tissue plasminogen activator (t-PA); Plasminogen Activator Inhibitor 1 (PAI-1); α2-antiplasmin (α2-AP); Thrombin-Activatable Fibrinolysis Inhibitor (TAFI).

stoichiometric complexes, induce conformational changes on their target proteases and make them irreversibly inactive. Next, within minutes to hours, these complexes are endocytosed and cleared by hepatic lysosomes, in this way reducing the protease molecules available to act on fibrin. PAI-1 is produced by hepatocytes, adipocytes, endothelium, and megakaryocytes, but platelet alpha-granules contain 90% of circulating PAI-1 (that is released upon platelet activation at the site of endothelial injury). The α2-AP is also produced in the liver. In situations in which the inhibitory capacity of α2-AP is exhausted (as frequently occurs in pharmacological thrombolysis, sustained bleeding and extensive

tissue injury), the role of α -2-macroglobulin as a ''rescue'' inhibitor of plasmin stands out.

PAI-1 and α2-AP are dispersed throughout in the plasma that permeates the fibrin mesh, so that they capture, respectively, the t-PA and plasmin molecules, as they escape the protection they receive while they are connected to the surface of the fibrin mesh. In addition to this fibrinolytic inhibition mechanism, these two inhibitors can also be incorporated into the structure of the fibrin mesh by Factor XIII (FXIII). In this position, they can act preventively against their target molecules before they can bind to the fibrin surface (at least in relation to α2-AP, this seems to be the most relevant mechanism of antifibrinolytic action).

In addition to PAI-1 and α2-AP, the Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) was recently identified. Pertaining to the group of carboxypeptidase enzymes, TAFI catalyzes the removal of lysine (or arginine) residues that are exposed on the fibrin surface as it is degraded by plasmin. TAFI suppresses the positive feedback on fibrinolysis described earlier by reducing the number of sites available for plasminogen binding to fibrin. TAFI is activated by the thrombin-thrombomodulin complex (and to a lesser extent by plasmin), and, together with thrombin, it connects coagulation and fibrinolysis. When there is scarce production of thrombin (as in hemophilia or acquired hemostasis disorders), TAFI activity decreases, favoring the activity of fibrinolysis, reduction in clot efficiency, and, eventually, bleeding. TAFI is also produced primarily by the liver and is also present in platelet alpha-granules (Figs. 1 and 5).

Thus, fibrinolytic activity is finely regulated at several points to limit fibrinolysis to the area of fibrin deposition and modulate its intensity, by:

- Confining plasmin production to the fibrin surface, after the formation of the ternary fibrin-plasminogen-t-PA complex. This precludes the occurrence of systemic hyperplasminemia, which would result in systemic fibrinogenolysis or, also, the lysis of other coagulation proteins by plasmin, such as factors V and VIII, Von Willebrand factor and platelet glycoproteins;
- Protection of plasminogen and its activators against inhibitors on the fibrin surface. This prevents fibrinolysis from being excessively inhibited, which could result in thrombotic complications;
- Relative abundance in the balance of inhibitors (synthesis, release, and clearance) in relation to activators;[1]
- Contribution of clot architecture on its susceptibility to fibrinolysis (described below);

Clot architecture and fibrinolysis

Irrespective of the intensity of fibrinolytic activity, clot lysis itself is also influenced by intrinsic features of the fibrin mesh, such as strength and firmness. These, in turn, are determined by the levels of thrombin, fibrinogen, platelets and FXIII.[7,8]

The higher the thrombin concentration, the thinner are the fibrin polymers produced; the same effect is observed with increasing concentrations of fibrinogen.[9] These thinner fibrin filaments tend to be lysed faster than the thicker ones. Conversely, meshes formed by more delicate fibers are more resistant to lysis, which is attributed to a higher density of filaments and less porosity. Meshes with smaller pores hamper the diffusion of solutes (such as t-PA and plasminogen) from the surrounding plasma to their binding sites on fibrin.[10]

One of the events resulting from endothelial injury is platelet activation, which involves, among other effects, the activation of glycoprotein IIb-IIIa (GPIIb-IIIa). Once activated, this surface glycoprotein can anchor fibrinogen molecules, ultimately resulting in the binding multiple adjacent platelets (a process called platelet aggregation). As fibrinogen molecules that bind to platelets are polymerised and converted to fibrin, these platelets become incorporated into the fibrin mesh. Physiologically, in the later stages of coagulation, activated platelets shrink their cytoskeleton. The intracellular filament network that composes the platelet cytoskeleton maintains connections with the intracellular face of GPIIb-IIIa, whose extracellular portion is responsible for binding the platelet to the fibrin mesh. In this way, when the cytoskeleton shrinks, this tension is transmitted to the fibrin mesh, inducing a denser packing of the clot volume. *In vivo*, this physiological change in clot architecture prevents vessel obstruction by the thrombus, strengthens the binding of the clot to with the vessel wall, brings vascular lesion edges closer together, reduces the likelihood of clot fragmentation, and attenuates fibrinolysis by hampering diffusion of plasmin to its binding sites within a more densely packed clot.[11] Thus, platelets appear to have a protective role against fibrinolysis by: (I) potentiating generation of thrombin (favoring greater production of FXIIIa and TAFI); (II) releasing FXIII, PAI-1 and fibrinogen from their granules; (III) retracting the clot, rendering it less susceptible to the action of plasmin.[7]

In the final steps of the coagulation process, factor XIIIa catalyzes the cross-linking of adjacent adjacent fibrin monomers, and incorporates α2-AP, PAI-1 and TAFI molecules into the fibrin mesh. Cross-linking makes the clot denser and more resistant to fragmentation, while the incorporation of inhibitors onto the fibrin mesh enables them to neutralize t-PA and plasminogen as soon as they get closer to the clot.

Perioperative fibrinolysis behavior

Blood vessel injury is omnipresent perioperatively and activates coagulation and fibrinolysis. Throughout a surgical procedure, the coagulation process usually stands out and tends to overshadow fibrinolysis that is occurring concurrently. Once surgical vascular injuries have ceased, clotting, within minutes to hours, progressively controls and suppresses the pathological events (that is, the exposure of subendothelial collagen) that had triggered itself. Henceforth, fibrinolytic activity – essentially secondary to the activation of coagulation – then becomes physiologically, clinically, and laboratory-wise more noticeable.

One of the earliest events in fibrinolysis is the secretion of t-PA by the damaged endothelium and its subsequent attachment to the fibrin mesh. Usually, in the following hours, the same injury that triggered t-PA secretion also leads to secretion of several cytokines by the injured tissues and to activation of the sympathetic system. Next, these secreted mediators stimulate the endothelial release of t-PA.[12] Thus, secondary fibrinolysis is usually a process that tends to last

hours after the action of coagulation, involving a set of physiological responses to tissue trauma. Within the first 24 hours, as tissue damage ceases and the levels of these mediators fall, fibrinolytic activity also undergoes a progressive reduction.[13]

Although this orchestrated activation between coagulation and fibrinolysis seems intuitive and represents the traditional understanding of hemostasis, recent studies have shown that these two physiological processes could act independently to each other.[14] Based on these findings, other authors have proposed that different patterns of injury could modulate the intensity of fibrinolysis activation into different phenotypes: hyperfibrinolysis, physiological fibrinolysis and fibrinolytic shutdown. In this last pattern, whose pathogenesis remains obscure, there would be resistance to the activation of fibrinolysis by t-PA, despite the activation of coagulation triggered by trauma.[15] Despite the potential clinical importance of this phenotype, especially regarding concerns on the use of antifibrinolytics in scenarios without a formal diagnosis of hyperfibrinolysis, further studies are required to define its role in the perioperative period.

Perioperative pathophysiology

In the perioperative scenario, changes in the fibrinolytic system with the greatest clinical relevance are those associated with excessive fibrinolysis. In this way, hyperfibrinolysis can be defined as an intensity of fibrinolysis that results in excessive bleeding (by premature lysis of fibrin contained in the hemostatic plugs). This process can occur systemically or locally, and the etiology can be congenital or acquired. Systemic hyperfibrinolysis has been divided from a clinical and mechanistic point of view into primary or secondary hyperfibrinolysis [16] (Fig. 6) However, as it is difficult to define which levels of fibrinolysis could be considered excessive, there is often a lack of uniformity in terminology among authors, so that these same phenomena are eventually called primary or secondary fibrinolysis,[17] having the prefix ''hyper'' suppressed from nomenclature.

Although, didactically, fibrinolysis subtypes have evident differences, in vivo, identifying the predominant mechanism may be difficult, due to existing physiological connections and overlaps among them. Thus, some clinical conditions often show potential for multiple mechanisms of hyperfibrinolysis (for example, severe trauma and cardiac surgery with CPB), frequently being hard to associate a condition with a single pathophysiologic mechanism.

Systemic primary hyperfibrinolysis

Systemic primary hyperfibrinolysis occurs in situations with an imbalance between activators and inhibitors of the fibrinolytic system (Table 1), generating a fibrinolytic activity that is excessive and unrelated to a coagulation system hyperactivity (i.e. there is a systemic hyperplasminemia). The imbalance intensity and, consequently, its clinical relevance, varies according to the severity of the triggering condition.

One chief mechanism generating a balance that favors fibrinolysis is the stimuli that stress the endothelium, and the most relevant perioperatively are vascular injury, hypoperfusion, hypoxia, acidosis, vascular stasis, and vasoactive substances (adrenaline, vasopressin, angiotensin, etc.). When present, they stimulate endothelial cells to secrete certain substances, among them, t-PA. Not rarely, several of these stimuli are commonly present in critically ill patients or in major surgeries, which may favor some degree of systemic hyperfibrinolysis in these patients.[12]

In cardiac surgery, some changes associated with cardiopulmonary bypass (release of adrenaline, angiotensin and vasopressin, risk of acidosis, hypoxia and hypotension, high plasmatic levels of kallikrein and bradykinin) also favor the endothelial secretion of t-PA unrelated to the production of thrombin or activation of coagulation. Such imbalance favoring fibrinolysis can be aggravated by the reduction of fibrinolysis inhibitor levels during CPB, which can be caused by the adsorption of these proteins to the extracorporeal circuit.[18]

Another relevant pathway is the acute coagulopathy associated with trauma and shock. The condition appears to be closely related to the effect of systemic hypoperfusion over the endothelium (commonly seen in traumas with severe bleeding).[19] Under hypoperfusion stress, besides secreting t-PA as previously described, endothelial cells increase the expression of thrombomodulin. This protein, in combination with thrombin produced by tissue injury, is able to activate circulating protein C. Then, activated protein C has its action amplified by protein S and inactivates PAI-1, the main antagonist of t-PA. In the scenario of severe trauma, t-PA secretion combined with the inactivation of PAI-1 potentiate themselves favoring systemic primary hyperfibrinolysis.[20]

Likewise, in orthopedic limb surgeries (forearm, hand, knee, and ankle), use of pneumatic tourniquets or the Esmarch band is common, resulting in hypoperfusion of the endothelial territory distal to compression. This induces endothelial release of fibrinolytic activators and, after tourniquet relief, they circulate and act systemically until they are cleared by the liver. In another example, in hip arthroplasties, the operated limb is adducted, flexed and rotated, and it is speculated that this maneuver could cause kinking of the proximal portion of the femoral vein, resulting in a mechanism similar to a tourniquet.[21]

In the harvesting process of solid organs, a period of ischemia starts after the donor cardiac arrest. This, as already explained, stresses the graft endothelium, whose response is intense t-PA secretion. During transplant surgery, after revascularization, t-PA from the implanted organ is released into the circulation of the recipient, inducing a state of intense fibrinolysis. The intensity of this systemic primary hyperfibrinolysis tends to be greater the greater the mass of the donated organ and the ischemia time, and the lower the hepatic clearance capacity of the recipient and the quality of organ preservation.[22]

Systemic secondary hyperfibrinolysis

Certain Disseminated Intravascular Coagulation (DIC) phenotypes and some situations of extensive tissue damage (such as major non-cardiac surgery, cardiac surgery, or severe trauma) share several clinical and laboratory features. So much so, that coagulation changes occurring in major surg-

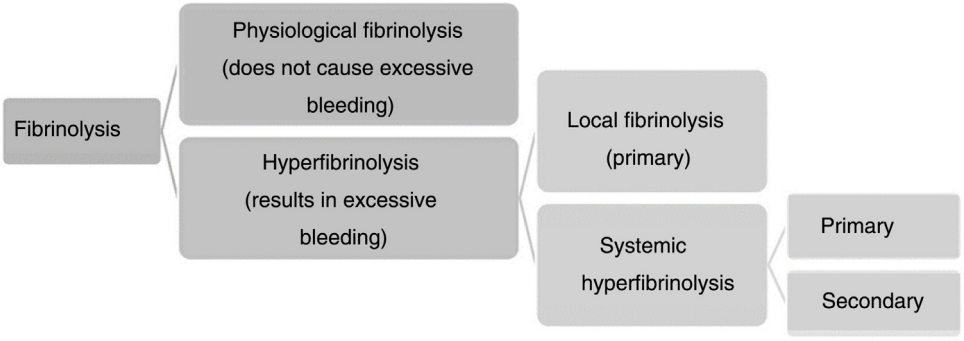

Figure 6 Classification proposed for fibrinolysis.

Table 1 Examples of scenarios compatible with systemic primary hyperfibrinolysis.

Systemic primary hyperfibrinolysis: imbalance between fibrinolytic system activators and inhibitors	
Origin of imbalance	Compatible scenarios
Increased endothelial production of activators (usually caused by endothelial stress)	Catecholamine, angiotensin, and vasopressin secretion bursts: shock scenarios, vasoactive drug use, electrical discharge Scenarios with hypoxia, hypoperfusion or acidosis: shock, cardiopulmonary arrest, intraoperative vascular clamping/ kinking, tourniquets applied on limb, thromboembolic vascular occlusions, transplant surgery (grafts are ischemic until they are implanted)
Activators arising from non-endothelial origin	Use of fibrinolytic drugs Organs for transplants Solid tumors expressing t-PA or u-PA
Failure to clear fibrinolytic activators	Severe liver disease or decreased hepatic blood flow Anhepathic phase during liver transplantation
Reduction of fibrinolytic inhibitors level	Severe liver disease or decreased hepatic blood flow Anhepathic phase during liver transplantation Extracorporeal circulation Acute traumatic coagulopathy

eries still are often classified as a DIC subtype,[23] but, for didactic purposes, we will maintain the distinction between these conditions.

In both conditions, there is excessive coagulation activation and deposition of fibrin inside vessels; in addition, thrombin itself (which mediates the conversion of fibrinogen to fibrin) stimulates endothelial t-PA secretion and fibrinolysis activation. However, the underlying difference is that, in major tissue damage, the activation of the fibrinolytic system is a strictly reactive physiological event and proportional to the activation of coagulation in traumatized or surgically injured tissues. Conversely, in patients showing DIC, the pathological triggering event generates a deregulation between coagulant and anticoagulant agents, which can result in thrombotic or hemorrhagic complications, with or without hyperfibrinolysis.[20,24] It should be underlined, however, that it is challenging to state, based on clinical and laboratory data, if there is equilibrium between coagulation and fibrinolysis (in other words, if there is DIC or only a physiological reaction to tissue damage).

At least on early stages, both situations evolve with a secondary physiological fibrinolysis. However, progressive depletion of fibrinogen, factors and platelets may occur in patients presenting intense and sustained clotting activation, especially when this is combined with major bleeding. Both these insults weaken the produced clot and make it more vulnerable to fibrinolysis, which can lead to excessive bleeding, a situation characterized as hyperfibrinolysis.[25] Furthermore, the low plasmatic physiological levels of α2-AP and its ''suicidal'' mechanism of action mean that prolonged fibrinolysis activation reduces the concentration of this component known as the main inhibitor of plasmin, systemically leading to a state of relative hyperplasminemia, and predisposing the patient to hyperfibrinolysis. Therefore, in prolonged coagulation activation scenarios, a mechanism which is initially reactional, proportional and physiological may become excessive (Table 2).

Cardiac surgery, in addition to the potential risk for primary hyperfibrinolysis already described, is also associated with significant activation of coagulation. Surgical damage exposes tissue factor and activates the extrinsic pathway, while contact of blood with the CPB circuit activates the intrinsic pathway. Thus, both pathways lead to some degree of thrombin production, even under heparinization. Thrombin, in turn, induces endothelial secretion of t-PA and activates the fibrinolytic system (systemic secondary fibrinolysis). In addition, as already described, the intrinsic pathway can activate plasminogen directly or favor

Table 2 Examples of scenarios compatible with systemic secondary hyperfibrinolysis.

Systemic secondary hyperfibrinolysis: clot weakening and exhaustion of fibrinolysis inhibitors after extreme and prolonged coagulation activation	
Mechanism	Compatible scenarios
Coagulation is activated anomalously and dissociatedly from fibrinolysis (DIC)	Sepsis Tissue factor-expressing neoplasms (mucinous adenocarcinomas, malignant brain tumors and acute promyelocytic leukemia) Obstetric complications (retained products of conception, pre-eclampsia, amniotic embolism, placenta praevia)
Major tissue damage causing intense, sustained and orchestrated activation of coagulation and fibrinolysis	Major trauma Major non-cardiac surgeries Major cardiovascular surgeries Postpartum hemorrhage (placental abruption, uterine atony or rupture, placenta praevia, placenta accreta)

its activation via t-PA and u-PA, also resulting in secondary fibrinolysis.

Another scenario that usually involves systemic primary and secondary hyperfibrinolysis is in the acute coagulopathy related to trauma and shock.[24] The primary hyperfibrinolysis mechanism occurs as previously explained. Systemic secondary fibrinolysis would occur physiologically following the coagulation activation caused by extensive tissue trauma.[20] Thus, elective surgeries with extensive tissue injury, such as spine or hip procedures, also seem to involve a predominantly secondary activation mechanism of fibrinolysis.

Some tumors, especially mucinous adenocarcinomas, hematological neoplasms, and malignant brain tumors are at high risk for thrombotic complications.[26] They can have anomalous expression of tissue factor on the surface of neoplastic cells. This provokes abnormal and unregulated activation of coagulation (DIC), often accompanied by laboratory findings of secondary hyperfibrinolysis.[27]

In certain causes of postpartum hemorrhage, such as uterine atony or abruptio placentae, there is excessive physiological activation of coagulation to control the endothelial rupture points, which is usually accompanied by secondary fibrinolysis. In other obstetric complications, such as retained products of conception, pre-eclampsia and amniotic embolism, there is unregulated activation of coagulation due to the release of massive amounts of procoagulant substances into the circulation, culminating in DIC and systemic secondary hyperfibrinolysis.

Local hyperfibrinolysis

Another relevant perioperative mechanism does not show either hyperplasminemia or systemic hyperfibrinolysis. It consists of an essentially primary and localized hyperfibrinolysis. It is caused by surgical or traumatic manipulation of tissues rich in fibrinolytic activators (t-PA and u-PA), leading to local release of these substances.[28] This seems to occur in ENT, and oral and maxillofacial surgeries, and in procedures involving the genitourinary tract, such as prostatectomies and myomectomies (Table 3).

In this way, lesions of certain tissues can trigger localized hyperfibrinolysis, dissolving thrombi at the site of the lesion, and eventually causing excessive bleeding, but do not show systemic laboratory markers of hyperfibrinolysis.[2,29] Due to technical challenges in the experimental investigation of fibrinolytic activity at the capillary level, the magnitude of the impact of this mechanism *in vivo* is merely presumptive,[30] based on the reduction of bleeding at certain sites after the use of antifibrinolytics in patients who had normal levels of systemic fibrinolystic parameters.[31]

Finally, it is important to highlight that the content of this section is solely a compilation of situations with the potential to present perioperative hyperfibrinolysis and that may be of interest to the anesthesiologist. Thus, the mere existence of a situation compatible with excessive fibrinolysis does not necessarily imply clinical relevance or require treatment.

Indications of antifibrinolytics versus mechanisms of hyperfibrinolysis

The perioperative use of antifibrinolytics can be analyzed observing the pathophysiological classification of fibrinolysis proposed in the previous section.[2]

At first, antifibrinolytics were developed for use in situations involving documented imbalance between activators and inhibitors of the fibrinolytic system, resulting in excessive systemic fibrinolytic activity as revealed by laboratory tests.[32,33] Thus, circumstances showing primary systemic hyperfibrinolysis, like those listed in the previous section, may be considered the classic indication of antifibrinolytics.

Local hyperfibrinolysis is also typically primary and constitutes another traditional antifibrinolytic indication;[34] however, as its mechanism is limited to the sites of trauma or surgery, this subtype of hyperfibrinolysis enables the topical use of antifibrinolytics. The efficacy of this administration route seems similar to that attained with systemic use[35] and, because it produces plasmatic levels up to 70% lower than equivalent intravenous doses,[36] topical use, in theory, would be associated with a lower risk for severe adverse effects.

For 30 to 40 years after their development, antifibrinolytics were used to treat the two mechanisms of hyperfibrinolysis described above in this section and showed efficacy and safety in reducing bleeding. Simultaneously,

Table 3 Examples of scenarios compatible with local hyperfibrinolysis.

Local hyperfibrinolysis: trauma or surgery on tissues rich in fibrinolytic activators (t-PA and u-PA), causing their local release	
Tissues	Bleeding scenarios with potential contribution of local fibrinolysis
Vascular endothelium of leptomeninges and choroid plexus	Bleeding after subarachnoid hemorrhage Traumatic brain injury Meningioma surgery
Oral and nasal mucosae	Adenoidectomy Tonsillectomy Oral cavity surgery Rhinoplasty and other nasal endoscopic surgeries Tooth extraction in hemophiliac patients or with von Willebrand disease
Eyes (Schlemm's canal endothelium)	Traumatic hyphema Eye trauma
Mucosa of the esophagus and stomach	Upper gastrointestinal bleeding
Genito-urinary tract	Surgery on the prostate, uterus, ovary, and bladder
Rectal mucosa	Lower gastrointestinal bleeding in patients with Crohn's disease or ulcerative colitis

evidence of the deleterious effects of bleeding and transfusions grew exponentially. Thus, at the turn of the past century, some authors began to evaluate the prophylactic use of antifibrinolytics, that is, in situations without an existing hyperfibrinolysis diagnosis, without occurrence of bleeding that could be attributed to hyperfibrinolysis, and without suspected imbalances in fibrinolysis activation or inhibition, either locally or systemically.[37] The claimed goal was simply to reduce bleeding by deliberately attenuating the physiological action of secondary fibrinolysis and, consequently, improving clot efficiency.

When the fibrinolytic balance is kept, a fibrinolytic process of physiological intensity occurs secondary to coagulation activation resulting from tissue trauma. As previously mentioned, as surgical injury and/or bleeding extend, a progressive exhaustion of endogenous inhibitors of fibrinolysis occurs, in addition to a weakening of clot structure. Consequently, in surgeries associated with extensive tissue damage and/or severe hemorrhage, an initially normal fibrinolysis may later become abnormal and exacerbate bleeding (secondary systemic hyperfibrinolysis).

The rationale for antifibrinolytic prophylactic use is to artificially reduce the physiological fibrinolysis, resulting in less bleeding and less depletion of factors, fibrinogen, and platelets. With such use, it is possible to prevent or postpone the development of hyperplasminemia, when the action of these drugs would then become therapeutic.

The prophylactic use of antifibrinolytics, by attenuating a strictly physiological mechanism, implies a theoretical risk of inducing hemostatic imbalances (such as thromboembolic events, for example). Several descriptions of thrombosis concomitant with the use of antifibrinolytics have already been reported, which have led several authors to consider contraindicating their prophylactic use on certain populations, such as: patients with a history of or predisposition to thromboembolic events; patients with cardiac, hepatic and renal comorbidities, and patients with coagulation disorders.[38] In such cases, therefore, it is recommended to individualize the risk assessment of possible thrombotic complications compared to the risks associated with major bleeding and massive transfusions.

On the other hand, studies with a more robust methodology, such as clinical trials and meta-analyses, have consistently demonstrated efficacy and safety in the prophylactic use of antifibrinolytics in the perioperative period over a wide range of doses and scenarios.[39] This apparently wide therapeutic margin was used as the foundation for guidelines that suggest the prophylactic use of antifibrinolytics in any surgery with predicted blood loss greater than 500 mL.[40]

However, regarding clinical trials evaluating antifibrinolytics, two cautions should be underlined: (I) their samples were not calculated to detect increases in the incidence of thrombotic events, but to detect differences in outcomes related to bleeding and transfusion; (II) most of the trials excluded patients with the relative contraindications mentioned above.[38] For this reason, the safety of these drugs in patients excluded from clinical trials is poorly understood. Recently, meta-analyses evaluating some studies that included these patients demonstrated similar incidence of adverse effects to those that excluded them,[41–43] raising questions about the need to exclude these patients in future trials. The favorable results in efficacy and safety for the prophylactic use of antifibrinolytics assigned them a central role in blood conservation programs, such as Patient Blood Management.[44]

Finally, it is worth underscoring that the therapeutic use of antifibrinolytics, that is, directed to treat laboratory-diagnosed fibrinolysis or a bleeding attributed to it, regardless of their underlying pathophysiological mechanism, is not subject to the contraindications previously discussed.

Recent large clinical trials

In the past decade, hundreds of clinical trials have assessed antifibrinolytics to mitigate bleeding (notably Tranexamic acid – TXA). Some of them, due to their methodological robustness and large sampling, eventually brought relevant impacts to current clinical practice.

In patients victims of trauma and with (or at risk for) significant bleeding – as indicated by systolic pressure less

than 90 mmHg and/or heart rate greater than 110 beats per minute – the CRASH-2 trial[45] demonstrated that TXA would be able to reduce overall mortality and bleeding, provided it is administered within 3 hours of trauma. In turn, the CRASH-3 study[46] investigated the TXA effect on intracranial bleeding after traumatic brain injury (patients with significant extracranial bleeding were excluded). Its results, when combined with data from other similar trials, demonstrated that TXA is safe in this scenario and reduces deaths related to traumatic brain injury, when administered within the same time interval employed in CRASH-2.

The TICH-2 trial evaluated TXA use after spontaneous intracranial bleeding[47] and a found reduction in hematoma expansion and in early mortality, but no improvement in patient functional status 90 days after the event. However, it is worth underlining that most patients only received TXA more than 3 hours after onset of the condition.

Recent studies have established both the therapeutic and prophylactic role of TXA for childbirth-related hemorrhage. The WOMAN trial[48] evaluated the impact of TXA on the postpartum hemorrhage scenario, defined by bleeding above 500 mL after vaginal delivery, C-section delivery bleeding above 1,000 mL or postpartum hemorrhage associated with hemodynamic instability. In these patients, when TXA was administered within 3 hours of delivery, there was a reduction in mortality due to bleeding and on requirements for laparotomy to control bleeding. Another obstetric study, the TRAAP trial,[49] evaluated TXA prophylactic use in vaginal delivery, right after the routine administration of oxytocin. In this study, the antifibrinolytic prophylactic use did not reduce the incidence of the primary endpoint (postpartum bleeding above 500 mL). None of the trials described in this section described increase in the incidence of thromboembolic events in patients receiving TXA.

Conclusions

Despite their importance, data on the mechanisms of normal and pathological functioning of fibrinolysis in the perioperative period have been fragmented and underestimated in the literature. For this reason, we believe that the information gathered here addresses a fundamental knowledge gap for the presumptive diagnosis and the management of perioperative fibrinolysis. Furthermore, by understanding the pathophysiological rationale supporting the indications for antifibrinolytics – therapeutic or prophylactic – anesthesiologists would expand the volume of information they possess to critically decide on the risk-benefit of antifibrinolytics.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Mutch N, Booth NA. Plasminogen activation and regulation of fibrinolysis. In: Marder VJ, Aird WC, Bennett JS, Schulman S, White GCI, editors. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. p. 314–33.
2. Stewart DB, Marder VJ. Therapy with antifibrinolytic agents. In: Marder VJ, Aird WC, Bennett JS, Schulman S, White GCI, editors. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. p. 918–30.
3. Sniecinski RM, Chandler WL. Activation of the hemostatic system during cardiopulmonary bypass. Anesth Analg. 2011;113:1319–33.
4. Bronisz M, Rosc D, Bronisz A, et al. The role of intrinsic fibrinolytic system activation in pathogenesis of hemostasis disturbances in hemodialyzed patients with chronic renal failure. Ren Fail. 2004;26:223–9.
5. Longstaff C, Thelwell C, Williams SC, et al. The interplay between tissue plasminogen activator domains and fibrin structures in the regulation of fibrinolysis: kinetic and microscopic studies. Blood. 2011;117:661–8.
6. Hoylaerts M, Rijken DC, Lijnen HR, et al. Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. J Biol Chem. 1982;257:2912–9.
7. Katori N, Tanaka KA, Szlam F, et al. The effects of platelet count on clot retraction and tissue plasminogen activator-induced fibrinolysis on thrombelastography. Anesth Analg. 2005;100:1781–5.
8. Dirkmann D, Gorlinger K, Gisbertz C, et al. Factor XIII and tranexamic acid but not recombinant factor VIIa attenuate tissue plasminogen activator-induced hyperfibrinolysis in human whole blood. Anesth Analg. 2012;114:1182–8.
9. yan EA, Mockros LF, Weisel JW, et al. Structural origins of fibrin clot rheology. Biophys J. 1999;77:2813–26.
10. Collet JP, Park D, Lesty C, et al. Influence of fibrin network conformation and fibrin fiber diameter on fibrinolysis speed: dynamic and structural approaches by confocal microscopy. Arterioscler Thromb Vasc Biol. 2000;20:1354–61.
11. Collet JP, Montalescot G, Lesty C, et al. Disaggregation of in vitro preformed platelet-rich clots by abciximab increases fibrin exposure and promotes fibrinolysis. Arterioscler Thromb Vasc Biol. 2001;21:142–8.
12. Francis CW, Marder VJ. Physiologic regulation and pathologic disorders of fibrinolysis. Hum Pathol. 1987;18:263–74.
13. Blanie A, Bellamy L, Rhayem Y, et al. Duration of postoperative fibrinolysis after total hip or knee replacement: a laboratory follow-up study. Thromb Res. 2013;131:e6–11.
14. Chin TL, Moore EE, Moore HB, et al. A principal component analysis of postinjury viscoelastic assays: clotting factor depletion versus fibrinolysis. Surgery. 2014;156:570–7.
15. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. J Trauma Acute Care Surg. 2014;77:811–7.
16. Kolev K, Longstaff C. Bleeding related to disturbed fibrinolysis. Br J Haematol. 2016;175:12–23.
17. Weisel JW, Litvinov RI. Mechanisms of Fibrinolysis and Basic Principles of Management. In: Saba HI, Roberts HR, editors. Hemostasis and thrombosis: practical guidelines in clinical management. Hoboken, NJ: John Wiley & Sons, Ltd; 2014. p. 169–85.
18. Despotis G, Eby C, Lublin DM. A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. Transfusion (Paris). 2008;48:2S–30S.
19. Kaczynski J, Wilczynska M, Fligelstone L, et al. The pathophysiology, diagnosis and treatment of the acute coagulopathy of trauma and shock: a literature review. Eur J Trauma Emerg Surg. 2015;41:259–72.
20. Cap A, Hunt BJ. The pathogenesis of traumatic coagulopathy. Anaesthesia. 2015;70 Suppl 1:96–101.
21. Eriksson BI, Hultman E, Martinell S, et al. Regional fibrinolysis following total hip replacement. Thromb Res. 1991;62:441–7.

22. Bakker CM, Metselaar HJ, Groenland TN, et al. Increased tissue-type plasminogen activator activity in orthotopic but not heterotopic liver transplantation: the role of the anhepatic period. Hepatology. 1992;16:404–8.
23. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care. 2014;2:15.
24. Gando S, Wada H, Thachil J, et al. Differentiating disseminated intravascular coagulation (DIC) with the fibrinolytic phenotype from coagulopathy of trauma and acute coagulopathy of trauma-shock (COT/ACOTS). J Thromb Haemost. 2013;11:826–35.
25. Weiskopf RB. The use of recombinant activated coagulation factor VII for spine surgery. Eur Spine J. 2004;13 Suppl 1:S83–8.
26. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. J Thromb Haemost. 2013;11:223–33.
27. Caine GJ, Stonelake PS, Lip GY, et al. The hypercoagulable state of malignancy: pathogenesis and current debate. Neoplasia. 2002;4:465–73.
28. Weitz JI. Overview of Hemostasis and Thrombosis. In: Hoffman R, Benz EJ Jr, Silberstein LE, Heslop H, Weitz JI, Anastasi J, editors. Hematology: Basic Principles and Practice. 6th ed. Philadelphia, PA: Saunders/Elsevier; 2013. p. 1774–83.
29. Bachmann F. Disorders of fibrinolysis and use of antifibrinolytic agents. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, editors. Williams Hematology. 6th ed. New York: McGraw-Hill; 2001. p. 1829–40.
30. Basu HK. Fibrin degradation products in sera of women with normal menstruation and menorrhagia. Br Med J. 1970;1:74–5.
31. Koh SC, Singh K. The effect of levonorgestrel-releasing intrauterine system use on menstrual blood loss and the hemostatic, fibrinolytic/inhibitor systems in women with menorrhagia. J Thromb Haemost. 2007;5:133–8.
32. Von Kaulla KN, Kaye H, von Kaulla E, et al. Changes in blood coagulation before and after hepatectomy or liver transplantation in dogs and man. Arch Surg. 1966;92:71–9.
33. Gans H, Krivit W. Problems in hemostasis during open-heart surgery. III. Epsilon aminocaproic acid as an inhibitor of plasminogen activator activity. Ann Surg. 1962;155:268–76.
34. Sack E, Spaet TH, Gentile RL, et al. Reduction of postprostatectomy bleeding by episilon-aminocaproic acid. N Engl J Med. 1962;266:541–3.
35. Montroy J, Hutton B, Moodley P, et al. The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis. Transfus Med Rev. 2018;32:165–78.
36. Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am. 2010;92:2503–13.
37. Neilipovitz DT, Murto K, Hall L, et al. A randomized trial of tranexamic acid to reduce blood transfusion for scoliosis surgery. Anesth Analg. 2001;93:82–7.
38. Gerstein NS, Brierley JK, Windsor J, et al. Antifibrinolytic Agents in Cardiac and Noncardiac Surgery: A Comprehensive Overview and Update. J Cardiothorac Vasc Anesth. 2017;31:2183–205.
39. Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. Br J Surg. 2013;100:1271–9.
40. Klein AA, Arnold P, Bingham RM, et al. AAGBI guidelines: the use of blood components and their alternatives 2016. Anaesthesia. 2016;71:829–42.
41. Khair S, Perelman I, Yates J, et al. Exclusion criteria and adverse events in perioperative trials of tranexamic acid in cardiac surgery: a systematic review and meta-analysis. Can J Anaesth. 2019;66:1240–50.
42. Yates J, Perelman I, Khair S, et al. Exclusion criteria and adverse events in perioperative trials of tranexamic acid: a systematic review and meta-analysis. Transfusion (Paris). 2019;59:806–24.
43. Sampaio AM, Guimaraes GMN, Medeiros GP, et al. [Efficacy and safety of antifibrinolytics in oncological surgery: a systematic review and meta-analysis]. Rev Bras Anestesiol. 2019;69:484–92.
44. Schoettker P, Marcucci CE, Casso G, et al. Revisiting transfusion safety and alternatives to transfusion. Presse Med. 2016;45:e331–40.
45. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376:23–32.
46. The CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;394:1713–23.
47. Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet. 2018;391:2107–15.
48. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389:2105–16.
49. Sentilhes L, Winer N, Azria E, et al. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. N Engl J Med. 2018;379:731–42.