Post-Operative Tromboembolism: New Therapeutical Prospectives

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Abstract

Despite the application of the thromboembolic prophylaxis, a residual risk of thromboembolic events persists after surgery. The knowledge of hemocoagulation system and its alterations secondary to the surgical trauma can allow understanding the reason why the risk of venous thromboembolism persists despite prophylaxis.

In the last years, interaction between hemocoagulation system and immune system has become increasingly a subject of study. Studies in the Literature confirmed that the hemocoagulative system is influenced and altered by both the surgical trauma and the post-operative activation of the immune system, thus worsening a pro-coagulant state.

Understanding all these mechanisms helps developing new strategies to reduce even more the risk of thromboembolism, and moreover to accomplish a proper anti-platelet therapy in patients with high risk of cardiovascular events candidate to surgical treatment.

Short Communication

Despite the application of a proper thromboprophylaxis according to the current guidelines [1], the risk of venous thromboembolism after surgery persists, ranging from 0.22% to 9.7% [2-6]. Post-operative alterations of the hemocoagulative parameters induced by surgical treatment in a pro-coagulant sense are well known and consist mainly in rising of D-dimer, prothrombin F1+F2, fibrinogenemia, platelet aggregation, PT, thrombin anti-thrombin complex. These alterations were more evident after open surgery than after laparoscopic surgery [7-11].

Laparoscopic surgery has been considered a procedure at low risk for developing thromboembolic events, because of a minor trauma and a faster patient’s mobilization, which counteract the effects of blood stasis in the lower limbs due to the anti-Trendelemburg position and to the pneumoperitoneum.

Although hemocoagulative alterations seemed to be proportional to the entity of the surgical trauma, studies about the medical and clinical differences during and after open and laparoscopic surgery revealed that other factors could enhance the hypercoagulable state.

Hitherward, an increasing interest about post-operative immune changes and interactions between hemocoagulative and immune systems after open and laparoscopic surgery can be found in the Literature [12-15].

In a prospective study, Dedej et al., [16] valuated the stress response to surgical trauma in term of alterations in coagulation’s parameters and their correlation with inflammation after laparotomy. They found a significant increase in the values of a PTT, fibrinogen, D-dimer and C-Reactive Protein (CRP) after surgery, and demonstrated that a hypercoagulable state that was amplified by inflammation. CRP is an opsonin whose role is to bind a specific protein expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system.

Schietroma et al., [17] in their prospective randomized study compared changes of the systemic inflammation and immune response in the early post-operative period after laparoscopic adrenalectomy performed with standard-pressure and low-pressure CO2 pneumoperitoneum. They observed that, although laparoscopy is ‘minimally invasive’, systemic immune response was activated. Patients who underwent open surgery showed a postoperative increasing of acute-phase proteins IL-1 and IL-6 higher than laparoscopic ones. IL-6 plays a central role in the acute phase of inflammation seen after surgery; since it induces the production of acute phase protein, such as CRP in hepatocytes.
A brief description of interactions between hemocoagulative and immune systems is reported below. The endothelial cell promotes a balance between antithrombotic and prothrombotic activity. In physiological conditions, the endothelial hemostatic balance leans more towards the production of antithrombotic factors. Tissue factor is expressed by the subendothelial vascular parietal cells and adventitious fibroblasts. Thus, the integrity of the endothelial surface prevents platelet deposition and adhesion. After damage of the vascular endothelium, it is exposed to the blood stream and acts as a key promoter of the hemocoagulative cascade and of inflammatory activity. Tissue factor forms a complex with activated factor VII, activating factors IX and X that culminates in the release of factor Xa. Factor Xa converts prothrombin into thrombin, activating the hemocoagulative cascade.

The modulation of the clot’s extension and the restoration of vascular integrity are mediated by the fibrinolytic system, which involves a distinct enzymatic cascade leading to the removal of fibrin deposits. The key component of the fibrinolytic system is plasminogen, which is activated in plasmin by two serin-proteases: the tissue plasminogen activator and the plasminogen urokinase activator. The first is involved in fibrinolysis, the second in the production of plasmin.

The fibrinolytic system modulates the immune system, is regulated by inflammatory mediators and is also recruited by pathogens, often to the detriment of the organism.

Plasmin is a potent proteolytic enzyme that breaks down fibrin clots in degradation products, which are chemo tactic for neutrophils. Plasmin also contributes to the inflammatory response by activating the classic complement pathway.

The complement is responsible for the amplification of the humoral immune response, and facilitates the elimination by the immune system of the foreign antigens bound to the antibodies.

Recent studies have shown that complement participates in several non-inflammatory processes, such as coagulation, hematopoiesis, reproduction, hepatic regeneration, apoptosis, homeostasis, metabolism and central nervous system development [18]. Platelet activation is also associated to the complement activation [19]. There is increasing evidence that the rapid activation of the coagulation cascade after trauma or sepsis is accompanied by an uncontrolled and progressive Systemic Inflammatory Response (SIRS), with often lethal consequences (Multi-Organ Dysfunction or MODS). Tissue trauma, acute blood loss and sepsis activate the complement cascade, whose activation level can determine the patient’s clinical outcome [20,21].

The hemocoagulation and immune systems activate locally in the site of the surgical trauma, promoting the tissue repair. As for the hemocoagulation system, the immune response to damaged cells and pathogens is immediate and local, thus limiting damage and promoting healing.

Unfortunately, either the hemocoagulative or the immune responses are not limited to the site of the surgical trauma. This condition may lead to thrombotic and/or inflammatory complications.

In the light of the current knowledge about the hemocoagulation system (Figure 1) and its interactions with the immune system (Figure 2), the perspective of new medicaments opens up with the purpose of further reducing the thromboembolic risk. Those medicaments may act at the level of the immune system, maybe where the immune system interact with the hemocoagulation system, preserving either the hemostatic function and the immunologic function, and avoiding at the same time side effects of their activation where it is not necessary. Possible targets for these future medicaments could be proteins linking the hemocoagulative system and the immune system.

The need not to disrupt hemostasis and the timing of administration must be taken into consideration, in order to have an adequate hemostasis, without the excess of thrombosis and, in extreme cases, of CID and MOFS.

Moreover, other new medicaments that can protect against thrombosis in patients at high cardiovascular risk who cannot interrupt their anti-platelet/anti-coagulant therapy in the peri-operative period may be conceived. Those medicaments must preserve the hemostatic function and avoid at the same time the hemorrhagic risk, which are fundamental for the success of the surgical procedure.

References


