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Mini Review

Use of antiplatelet agents in sepsis: A glimpse into the future

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ABSTRACT

As mechanisms of sepsis pathophysiology have been elucidated with time, sepsis may be considered nowadays, as an uncontrolled inflammatory and pro-coagulant response to a pathogen. In this cascade of events, platelets play a key role, via interaction with endothelial cells and modulation of both innate and adaptive immune system. In that manner, inhibition of platelet function could represent a useful tool for attenuating inflammatory response and improving outcomes. Data on current antiplatelet agents, including acetylsalicylic acid, P2Y12 inhibitors and GPIIb/IIIa antagonists, in animal models are promising. Clinical data in patients hospitalized for pneumonia, at risk for acute lung injury, and/or critically ill revealed an association between antiplatelet therapy and reduction in both short-term mortality and prevalence of acute lung injury, as well as, the need for intensive care unit admission, without a concomitant increased bleeding risk. In need of innovative approach in the treatment of sepsis, further prospective, interventional, randomized trials are pivotal to establish potential use of antiplatelet agents in this context.

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Introduction

Sepsis is a prevalent syndrome that carries significant morbidity and mortality. Almost 24% of patients with an admission diagnosis of sepsis will progress to severe sepsis with an associated 35–50% mortality rate [1,2]. As a result, an estimated economic burden of nearly 17 billion dollars annually in the USA, has currently been attributed to sepsis [1].

Activation of blood platelets is a typical finding in patients with systemic inflammation and sepsis, while thrombocytopenia in critically ill

Abbreviations: ADAMTS-13, A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13; ADP, Adenosine Diphosphate; ATP, Adenosine Triphosphate; ALI, Acute Lung Injury; ARDS, Acute Respiratory Distress Syndrome; ASA, AcetylSaliculic Acid; ATL, 15-epi-lipoxin A4; CABG, Coronary Artery Bypass Grafting; CAP, Community Acquired Pneumonia; COX, CyclOXygenase; CRP, C-Reactive Protein; C4b, complement component 4b; DIC, Disseminated Intravascular Coagulation; eNOs, endogenous nitric oxide synthase; Erk1, extra cellular signal kinase 1; GP, GlycoProtein; ICU, Intensive Care Unit; IL-#, InterLeukine #; IL-10r, InterLeukine 10 receptor; iNOs, inducible nitric oxide synthase; LPS, LipoPolySacccharide; Ltb4r, LeukoTriene b4 Receptor; MIP-1a, Macrophage inflammatory protein-1alpha; MOF, Multiple Organ Failure; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NET, Neutrophil Extracellular Trap; NO, Nitrogen Oxide; PAF, Platelet Activating Factor; PLATO, PLATelet inhibition and clinical Outcomes; PMN, PolyMorphoNuclear cells; PSGL-1, P-Selectin Glycoprotein Ligand-1; RANTES, Regulated on Activation, Normal T cell Expressed and Secreted; ROS, Reactive Oxygen Species; SIRS, Systemic Inflammatory Response Syndrome; TCR, T-Cell Receptor; TF, Tissue Factor; TLR, Toll-Like Receptor; TNF alpha, Tumor Necrosis Factor alpha; vWF, von Willebrand Factor.

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patients is associated with poor outcome [3–5]. It has been well established that platelets significantly contribute to organ failure via their haemostatic and thrombotic potential, resulting in thrombotic microangiopathy and disseminated intravascular coagulation. What is less known however, is their involvement in the adaptive immune response [6] as well as, their interaction with microorganisms [7]. A number of agents including corticosteroids, tumour necrosis factor (TNF)-alpha antagonists and interleukin 1 (IL-1) receptor antagonists, have been suggested to potentially block the inflammatory cascade, prevent severe sepsis and ensure better outcomes, [8]. Although data from phase II clinical trials showed promise, larger studies have not demonstrated any significant improvement in clinical outcomes [8].

Antiplatelet drugs including acetylsalicylic acid (ASA), and P2Y12 inhibitors are widely used in patients with cardiovascular disease for the secondary prevention of atherothrombotic events [9]. Several studies have shown that ASA and clopidogrel not only diminish the risk of atherothrombotic events, but also reduce markers of systemic inflammation, including C-reactive protein (CRP), soluble CD62P (P-selectin) and CD54, pro-inflammatory cytokines, and platelet-leukocyte conjugates [10]. It is assumed that the anti-inflammatory effects of antiplatelet drugs are mediated by an inhibition of platelet activation [10]. Thus, derived by the need to extend current pharmacological treatment options, the question arises, whether drugs that inhibit platelet activation, such as ASA or P2Y12 inhibitors, may have a benefit in critically ill patients.

This review will highlight current data on potential use of antiplatelet agents in managing sepsis.

Role of Platelets in Sepsis

There is substantial evidence that blood platelets play an important role in the development of multiple organ failure (MOF) in septic patients [4,5]. During infection and systemic inflammation, platelets become activated, as reflected by an increase in the number of CD62P-positive platelets and platelet-leukocyte conjugates [3,5]. Different mechanisms have been associated with platelet activation, including imbalance between plasma level of high molecular weight von-Willebrand factor and - its cleavage protease - a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13), and binding of endotoxins to specific receptors at the platelet surface [5,11]. Once activated, the platelet alters from its normal disc-like shape to a more spherical appearance with arm-like extensions, that facilitate adhesion to the endothelium and to other cells [11]. Platelet/endothelium interaction plays a central role in inflammatory mechanisms within the vessel wall [12]. It has been reported that activated platelets - as occurs in endotoxemia - aggregate and can bind to endothelial cells, despite the presence of intact endothelium [11,13,14]. Platelet adhesion to endothelium enhances the procoagulatory activity of endothelial cells, subsequently impairing microcirculation and, thus, leading to hypoperfusion and organ dysfunction [11,15].

Platelet activation also causes the expression of cell surface receptors and release of molecules that can amplify the immune response [11]. Namely, the initial interactions are driven by P-selectin (CD62P) on the surface of activated platelets, which is recognised by P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes [3,5,11,16]. Functional cross talk between the P-selectin-PSGL-1 pair and the leukocyte integrin $\alpha_M\beta_2$ (Mac-1) orchestrates the molecular events necessary for leukocyte recruitment, via platelet activation and the subsequent vascular response to injury [6,11,16]. Adhesion of platelets to monocytes results in signalling dependent transcriptional regulation, which leads to expression of important mediators of inflammation and pro-coagulant tissue factor (TF) [11]. Platelet surface expression of CD40L (CD154) and its subsequent binding to the CD40 receptor may also be involved in immune cell recruitment, chemokine production, IgM to IgG isotype switching, and dendritic cell maturation [11].

Furthermore, platelets express toll-like receptors (TLRs), pathogen recognition receptors involved in activation of innate immunity, including TLR2 and TLR4 that recognize the common bacterial molecules peptidoglycan and lipopolysaccharide (LPS), respectively [11]. Interactions between platelet TLR4 and LPS may contribute in thrombocytopenia in sepsis and pulmonary fibrin deposition [11]. Activated platelets, particularly in the context of LPS stimulation, trigger the release of extracellular DNA traps (NETs) with proteolytic activity from neutrophils, serving to capture and degrade microbes [11]. Thus, immune-mediated effects of platelets may be important for the host defence.

At the same time, platelet activation exacerbates the release of more than 35 distinct, active compounds that are capable of modulating not only their own function, but also that of cells around them [4,6,11]. Platelet alpha granules contain chemokines and other soluble mediators of inflammation such as IL-1b, regulated on activation normal T cell expressed and secreted protein (RANTES), macrophage inflammatory protein (MIP-1 alpha), monocyte chemo-attractant protein, thymus and activation-regulated chemokine, and antimicrobial defensins (thrombocidins) involved in coagulation pathways or stimulating further platelet recruitment and attracting neutrophils and leukocytes, which are key players in mediating ongoing inflammatory responses such as sepsis [4,6,11]. Among them, the potent serine protease granzyme B is expressed, resulting in cytotoxic platelets mediating apoptosis in lung and spleen tissue [17]. Fig. 1 summarizes current examples of activated platelets mediating immune responses.

However, the effects of certain bacterial products on platelet function have not been found to be consistent and may vary according to species, timing of the study, location of platelets in the circulation, and pathogenesis of sepsis [18–20]. For example, LPS has been shown to increase platelet aggregation in various animal models [21–23], yet bacterial products seem to decrease human platelet aggregation *in vitro* [24,25]. In a small group of 74 patients with sepsis and severe sepsis Mavromattis et al. [26] showed that platelet aggregation increased somewhat in patients with an uneventful course but decreased over time in patients who developed severe sepsis. Similarly, in a series of 26 patients Boldt et al. noted decreased platelet aggregation in critically ill patients, as later confirmed by others at a molecular level [18,27]. However, Gawaz et al. [19] described increased adhesion and activation of platelets, even in patients in an intensive care unit (ICU).

Antiplatelet Agents in Sepsis

Acetylsalicylic Acid (ASA)

Endothelial dysfunction is one of the early signs of a systemic inflammatory reaction and is believed to be one of the triggers of organ failure in sepsis [15]. ASA stimulates the synthesis of 15-epi-lipoxin A4 (ATL), which in turn increases nitric oxide synthesis through endothelial and inducible nitric oxide synthase [28]. Nitric oxide inhibits the interactions between leucocytes and endothelial cells, resulting in decreased polymorph neutrophil recruitment [28] (Fig. 2). Contrary to findings in models of endotoxemia [29,30], low doses of aspirin seem to inhibit platelet activation and have anti-inflammatory effects in patients with coronary heart disease. The latter include decrease in the expression of pro-inflammatory mediators including TNF, IL-6, TF, or up-regulation of NFkB, a central transcription factor in inflammation and cell death regulation.[10] (Fig. 2).

Several studies evaluating aspirin for the treatment of sepsis in animal models, have suggested a potential benefit [31,32]. Recently, Derhaschnig et al. [33] evaluated the effects of aspirin and a nitroderivative of aspirin (NCX-4016) on platelet function in healthy volunteers after infusion of endotoxin. NCX-4016 acts through COX inhibition and nitric oxide release, thus, reducing thrombin induced platelet activation more effectively than ASA [34,35]. Interestingly, while NCX-4016 had virtually no effect on platelet function, aspirin