Thrombosis Research 166 (2018) 28–36

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Platelet activation and antiplatelet therapy in sepsis: A narrative review☆

Yuhui Wang, Yaqi Ouyang, Baoyan Liu, Xiaochun Ma, Renyu Ding*

Department of Intensive Care Unit, The First Hospital of China Medical University, Nanjing Bei Street 155, Shenyang 110001, Liaoning Province, PR China

ARTICLE INFO

Keywords:
Sepsis
Platelet activation
Antiplatelet drugs
Aspirin
Clopidogrel

ABSTRACT

Platelet activation plays an important role in the development of sepsis. During sepsis, platelet activation leads to endothelial cell injury and promotes neutrophil extracellular trap and microthrombus formation, exacerbating septic coagulation and inflammatory reactions. The resultant induction or aggravation of disseminated intravascular coagulation (DIC) leads to organ damage. Antiplatelet drugs can inhibit coagulation and inflammatory reactions in models of sepsis, reducing damage to organ function. Clinical studies suggest that aspirin may improve the prognosis of patients with sepsis. In conclusion, antiplatelet drugs are promising agents that can improve the prognosis of sepsis patients and are expected to become a new line of treatment. However, further clinical studies are required for validation.

1. Introduction

Sepsis is characterized by complex pathological mechanisms and has a high mortality rate [1]. In 1991, a consensus conference proposed the initial definition of sepsis as “a host's systemic inflammatory response syndrome (SIRS) to infection” [2]. In 2016, a new sepsis definition was developed as “a life-threatening organ dysfunction caused by a dysregulated host response to infection” [3]. The new definition of sepsis shifts emphasis from SIRS to organ dysfunction. For many years, there have been numerous studies on sepsis, but treatment outcomes have been less than ideal. Sepsis and the concomitant multi-organ dysfunction are still the primary causes of death in seriously ill patients [4]. In recent years, an increasing number of studies have shown that platelets participate in the pathophysiological processes of sepsis and play an important role in organ damage [5,6]. When pathogens invade the body, activation of the coagulation system at the site of infection and thrombus formation in local capillaries serve as defense mechanisms that limit the infection to the lesions by a process known as immune thrombosis [7]. In sepsis, these local reactions spread to the entire body, and a loss of control of the “inflammation-coagulation” interaction leads to disseminated intravascular coagulation (DIC) and subsequent multi-organ dysfunction syndrome (MODS). Inflammation-coagulation reactions in sepsis and damaged endothelial cells induce platelet activation, and these activated platelets can further exacerbate the systemic inflammatory reactions and coagulation disorders through interactions with inflammatory and endothelial cells, as well as through other mechanisms [8–10]. Thus, inhibiting platelet activation may reduce the uncontrolled inflammatory and coagulation reactions in sepsis, alleviate the severity of organ damage, and improve the prognosis of sepsis.

2. Methods

We searched the MEDLINE and Web of Science databases for English-language sources using the following keywords: platelet activation, platelet function, antiplatelet, platelet inhibitor, aspirin, acetylsalicylic acid, clopidogrel, sepsis, and septic shock. Clinical studies published before July 2017 were selected if they (1) included patients receiving antiplatelet therapy and were compared with a placebo or no antiplatelet treatment, (2) included the clear diagnostic criteria for sepsis, and (3) reported mortality as a consequence of the sepsis episode (selected studies are shown in Table 1). Non-adult studies were excluded.

Abbreviations: ADP, adenosine diphosphate; APC, activated protein C; AT-III, antithrombin III; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CLP, cecal ligation - perforation; DIC, disseminated intravascular coagulation; LPS, lipopolysaccharide; IL-1, interleukin-1; MODS, multi-organ dysfunction syndrome; MCP-1, monocyte chemoattractant protein 1; NETs, neutrophil extracellular traps; NF-κB, nuclear factor-κB; NK cell, natural killer cell; NO, nitric oxide; PAF, platelet-activating factor; PAR), protease-activated receptor; PF4, platelet factor 4; PSGL-1, P-selectin glycoprotein ligand 1; SIRS, systemic inflammatory response syndrome; sTLT-1, soluble triggering receptor expressed on myeloid cells (TREM)-like transcript-1; TLR, Toll-like receptor; TXA2, thromboxane A2; TF, tissue factor; TFPI, tissue factor pathway inhibitor; VCAM-1, vascular cell adhesion molecule-1; vWF, von Willebrand factor

☆ The authors have not disclosed any potential conflicts of interest. No part of text and graphics has been recycled from elsewhere.

* Corresponding author.
E-mail address: renyuding@126.com (R. Ding).

https://doi.org/10.1016/j.thromres.2018.04.007
Received 4 January 2018; Received in revised form 3 April 2018; Accepted 6 April 2018
Available online 09 April 2018
0049-3848/

Table 1
Clinical studies on the effects of antiplatelet therapy on the prognosis of sepsis.

Number	Year of publication	Study design	Patient type	Intervention	Primary outcome	Number of patients	OR	95% CI	*P* value	Evaluation of quality	Reference
1	2012	Retrospective	ICU admission with severe sepsis or septic shock	Aspirin medication during ICU stay	ICU mortality	834	0.55	0.38–0.81	< 0.01	Aspirin may reduce ICU mortality	Lösche, et al. [5]
2	2012	Retrospective	ICU patients with proven sepsis	Aspirin (administered within 24 h of onset of SIRS)	Hospital mortality	970	0.606	0.515–0.714	< 0.001	A significantly lower mortality with Aspirin-treatment	Eisen, et al. [67]
3	2015	Retrospective	ICU admission with sepsis	Aspirin received before ICU admission	Hospital mortality	218	1.049	0.299–3.685	> 0.05	No significant benefit with aspirin therapy	Campbell, et al. [68]
4	2016	Retrospective	ICU admission with sepsis	Aspirin received during ICU stay	Adjusted hospital mortality	194	0.89	0.41–1.93	0.16	Aspirin does not lower mortality but rather increases the risk of ICU acquired severe sepsis	Al Harbi, et al. [69]
5	2013	Retrospective	ICU admission with severe sepsis or septic shock	Aspirin (received at least at two days during the ICU stay with 100 mg/d of aspirin)	ICU mortality Hospital mortality	886	0.56 0.57	0.37–0.84 0.39–0.83	0.005 0.003	low-dose Aspirin may be beneficial in the treatment of sepsis	Otto, et al. [70]
				Clopidogrel (received at least at two days during the ICU stay with 75 mg/d of clopidogrel)	ICU mortality Hospital mortality		1.27 1.65	0.67–2.41 0.91–3.01	0.467 0.101		
6	2013	Retrospective	ICU admission with severe sepsis or septic shock	Antiplatelet (at the time of ICU admission)	Hospital mortality	651	0.73	0.46–1.16	0.19	Antiplatelet therapy before the diagnosis of severe sepsis or septic shock does not decrease hospital mortality	Valerio-Rojas, et al. [72]
7	2015	Retrospective	Hospitalized for sepsis	Antiplatelet (currently or within 30 days before ICU admission)	Hospital mortality	683,421	0.82	0.81–0.83	< 0.001	Prior use of antiplatelet agents is associated with survival benefits in sepsis patients	Tsai, et al. [73]
8	2016	Prospective	ICU admission with sepsis	Antiplatelet therapy (95.9% acetylsalicylic acid) before ICU admission	30-day mortality	972	1.22	0.88–1.7	0.23	Did not find an association between chronic antiplatelet therapy and severity of illness or outcome.	Wiewel, et al. [74]

ICU, intensive care unit; OR, odds ratio; CI, confidential interval.