STUDY OF PROTEIN C, PROTEIN S AND ANTITHROMBIN III IN SEPTIC NEWBORNS

Thesis

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ABSTRACT

Study of protein c, protein s and antithrombin III in septic newborns

(KEY WORDS): Neonatal sepsis , Protein C , Protein S , Antithrombin III,Disseminated intravascular coagulation (DIC), Physiologic inhibition system of coagulation.)

Neonatal sepsis is a major cause of neonatal mortality and morbidity. Sepsis greatly affects the coagulation system of the affected neonates. We measured protein c, protein s and antithrombin III levels in thirty septic neonates and thirty normal neonates served as control group. The study revealed the effect of decreased levels of the physiologic inhibition system of coagulation (PISC) including protein c, protein s and antithrombin III on further development of thromboembolic complications in septic neonates, as 30% of the studied cases developed disseminated intravascular coagulation (DIC). Protein C concentrates can act as adjuvant therapy to antibiotics.

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LIST OF ABBREVIATIONS

A … … …. …. … … … Activated factor

ALT….. ……. ……. Alanine aminotransferase

APC ……. Activated protein C

AST ……. Aspartate aminotrasferase

ATIII…… Antithrombin III

DIC ……. Disseminated intravascular coagulation

Drot AA……. Drotrecogin alpha activated

EPCP … … … … … … Endothelial cell protein C receptor

F… ….. …… ……. …. Factor

FDP… … … … … … … Fibrin degradation product

GBS… …. …. …. …. … Group B streptococcus

HB ……. Haemoglobin

HCT……. Haematocrite

NEC……..Necrotizing enterocolitis

PC…… Protein C

P.Fulminans……Purpura Fulminans

PS…… Protein S

PISC…….. Physiologic inhibition system of coagulation

PROM…….. Prolonged rupture of membranes

PT …… Prothrombin time

PTT…… Partial activated thromboplastin time

Rh-APC……. Recombinant human activated protein c

TM … … … … … … … Thrombomodulin

TPF …… Tissue factor pathway

INTRODUCTION

The perinatal period is associated with an increased incidence of thromboembolic complications, which may occur in both the maternal and the fetal circulation in otherwise normal and healthy adults and fetuses, and this may be related to the activation of the coagulation system at the time of parturition. The risk of these complications is generally much higher in neonates, who have decreased activity of the physiologic inhibition system of coagulation (PISC), including protein C, protein S, and antithrombin III in comparison with adults, thus predisposing neonates to thromboembolic complications ***(Malida et al, 2002)*.**

The hemostatic system of the fetus and of the neonate is dynamic. Coagulation and inhibitory factors of coagulation are progressively synthesized by the fetus beginning mainly after 34 weeks of gestation and into the first hours following delivery, guaranteeing the presence of a sufficient hemostatic balance at birth. At term, most fetal plasma factors of coagulation, including vitamin K-dependent factors, contact factors and the physiologic inhibition system of coagulation (PISC), are obviously immature and have not yet reached adult plasma concentrations ***(Malida et al, 2002)*.**

Sepsis has emerged as one of the most crucial factors influencing the mortality and morbidity of the newborn and preterm infant in intensive care units ***(Kreuz et al, 1999)*.**

A number of life threatening pathologic processes including sepsis, septic shock, hypoxia, acidosis, tissue necrosis and endothelial damage may trigger DIC ***(Behrman and Kleigman, 2004)***. In these newborns, sepsis and septic shock, as a progressive state of poor tissue perfusion, leads to severe metabolic derangements and organ failure during overwhelming infection. The underlying pathophysiology is a combination of irreversible hypotension and obstructed flow because of microthrombus formation in the capillary system ***(Bone, 1994)***. Whereas the former is mainly a direct response to endotoxin, microcirculatory thrombosis is the result of multiple pathway activation as a systemic response to infection, termed systemic inflammatory response syndrome (SIRS) ***(Suffredini et al., 1990)***.

Because of hypoxia which has been proven to decrease the levels of protein C, protein S and antithrombin III ***(El-Beshlawy et al., 2004)***, physiological cardiopulmonary overload, and other neonatal disorders, newborns and preterm infants are predisposed to disturbances of the peripheral circulation. Therefore the vascular endothelium of these patients is especially vulnerable in maintaining hemostasis, leading to early association of sepsis and DIC ***(Leithauser et al., 1996)***.

There is a large body of evidence that the hemostatic system of the newborns and pretem infant is generally shifted towards hypercoagulation. During sepsis this hypercoagulability is further exacerbated by affecting the coagulation and the inhibitory factors of

coagulation including protein C, protein S and antithrombin III ***(Roman et al., 1992)***.

Sepsis is considered an acute stressor that was found to alter coagulation system equilibrium ***(Andrew, 1997).***

AIM OF THE WORK

This study aims to clarify the effect of sepsis on the physiologic inhibition system of coagulation including protein C, protein S and antithrombin III and their effect on thromboembolic accidents of septic newborns.

REVIEW OF LITERATURE

ROLE OF PROTEIN C, PROTEIN S AND ANTITHROMBIN III IN HAEMOSTASIS IN THE PEDIATRIC AND NEONATEAL AGE GROUP

Haemostasis is one of a number of protective processes that have evolved in order to maintain a stable physiology. It has many features in common with (and to some extent interacts with) other defence mechanisms in the body, such as the immune system and the inflammatory response. These links are most clearly seen in ancient species such as the horseshoe crab (Limulus polyphemus), where a primitive 'coagulation' pathway is initiated by entry of endotoxin into the haemolymph. Vestiges of this process still exist in humans and may give rise to serious clinical consequences. For example, disseminated intravascular coagulation (DIC) can be initiated by Gram-negative septicemia. However, consequent upon the development of a high-pressure blood circulatory system, extra components have evolved and have resulted in a complex, highly integrated process in all vertebrates. Indeed, recent analysis of the haemostatic network in bony fish suggests that the network in its entirety evolved over 430 million years ago, prior to the divergence of bony fish from tetrapods **(Dahlback and Villoutreix, 2003).**

The high blood pressure generated on the arterial side of vertebrate circulation requires a powerful, almost instantaneous but strictly localized

procoagulant response in order to minimize blood loss from sites of vascular injury without compromising blood flow generally. Systemic anticoagulant and clot-dissolving components have also evolved to prevent extension of the procoagulant response beyond the vicinity of vascular injury resulting in unwanted thrombus formation in the slow, sometimes intermittent, blood flow in the veins. The resultant haemostatic system is thus a complex mosaic of activating or inhibitory feedback or feed-forward pathways, integrating its five major components (blood vessels, blood platelets, coagulation factors, coagulation inhibitors and fibrinolytic elements). Furthermore, links between haemostasis and other elements of the body's overall defence response, such as the complement and kinin-generating processes and phagocytosis, must also be considered **(Dahlback and Villoutreix, 2003).**

In the most simplistic terms, blood coagulation occurs when the enzyme thrombin is generated and proteolyses soluble plasma fibrinogen, forming the insoluble fibrin polymer, or clot; this provides the physical consolidation of vessel wound repair following injury. Haemostasis' refers more widely to the process whereby blood coagulation is initiated and terminated in a tightly regulated fashion, together with the removal (or fibrinolysis) of the clot as part of vascular remodelling; as such, haemostasis describes the global process by which vessel integrity and patency are maintained over the whole organism, for its lifetime **(Dahlback and Villoutreix, 2003).**

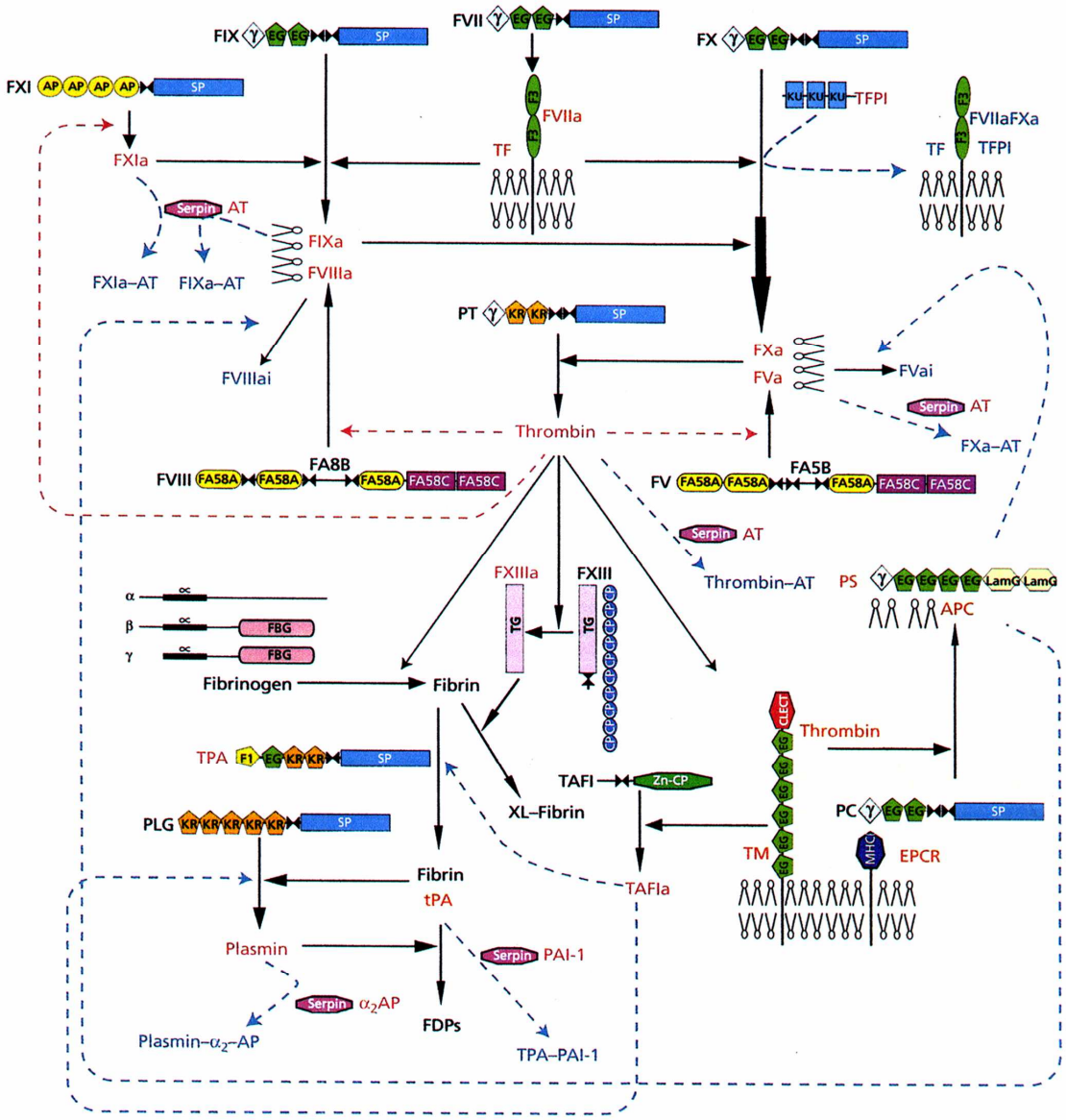

Fig (1): Mechanism of inhibition of coagulation cascade from (Kemball-Cook and Tuddenham et al.: Normal haemostasis :In Postgraduate Haematology edited by A. Victor Hoffbrand, Daniel Catovsky, Edward G.D. Tuddenham: Fifth Edition, 2006.)