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Pentoxifylline Lifts the Burden of Preeclampsia

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Abstract

Worldwide, Preeclampsia is the leading cause of maternal morbidity and perinatal mortality and it initiates as inappropriate immune response to trophoblastic invasion impairs placentation and placental circulation followed by generation of superoxide anions as well as anti-angiogenic factors and this series of events result in impairment of maternal/placental endothelial function, maternal hypertension, kidney injury, proteinuria and thromboembolic events. Renal loss of anti-coagulant proteins and subsequent hyper-coagulable state along with endothelial dysfunction accelerates progression of the disease toward eclampsia. Pentoxifylline, could hypothetically modify pathophysiological mechanisms of preeclampsia including impaired immune response, placentation, endothelial function and coagulation, so it could explore new horizons in treatment of preeclampsia.

Keywords: Pathophysiology; Pentoxifylline; Placentation; Preeclampsia

Introduction

Hypertensive pregnancy disorders are among the most common complications of pregnancy and almost 10% of all pregnant women experience a variety of these disorders [1]. Preeclampsia is one of these varieties and it affects 3-5% of all pregnancies and it is estimated to cause 60,000 maternal deaths annually worldwide [2,3]. Preeclamptic patients are at increased risk for delivering newborns who are small for their gestational age (SGA), placental abruption, pretermlabor developing end-stage renal disease (ESRD), cardiovascular and cerebrovascular diseases and preeclampsia is the leading cause of maternal morbidity and perinatal mortality [4-8]. Four major pathophysiological mechanisms of the disease include abnormal immune response, defects through placentation, endothelial dysfunction and hypercoagulability [9].

Physiologically, in pregnancy, immune reactions shift towards T helper type-2 (Th2) mediated immune responses [10] while T helper type-1 (Th1) is the dominant effector in pre-eclamptic pregnancies. Increased production of Th-1 activator cytokines such as Interleukin 1 beta, Interleukin 2, Interleukin 6, Interferon ϒ, Tumor Necrosis Factor α and decreased production of Interleukin 10, shifts the immune system toward Th-1-mediated immune responses and impairs the placentation followed by poor placental perfusion [11]. Intermittent disturbances of placental perfusion results in ischemia-reperfusion injuries, formation of superoxide anions and endothelial dysfunction. Furthermore the placenta excretes anti-angiogenic factors (sFLT-1 and sEndoglin) and impairs both maternal and placental endothelial function and angiogenesis/angioregeneration [12]. Endothelial formation of NO and prostacyclins is decreased while release of endothelin and Thromboxane is increased. Such changes result in vasoconstriction, increased coagulability and increased glomerular permeability and proteinuria [13]. As albumin is secreted in urine, the hypo-albuminemia and further peripheral edema impairs Renal Plasma Flow (RPF) and subsequent activation of RAAS (Renin-Angiotensin-Aldosterone System) intensifies vasoconstriction/hypertension and increases Na^+/H_2O retention, which worsens the edema and a vicious cycle ensues [9]. Loss of antithrombotic proteins by kidneys, together with decreased endothelial formation of NO and increased endothelial release of Thromboxane and Plasminogen Activator Inhibitor (PAI) result in a hypercoagulable state and accelerates progression of preeclampsia toward eclampsia [14].

Doppler ultrasonography is a useful noninvasive method to detect high risk individuals in first and second trimester. Assessing uterine artery by Doppler velocimetry could demonstrate the extent of trophoblastic invasion and reconnoiter high risk individuals [15,16]. There are also many factors in maternal serum and urine which may predict incidence of preeclampsia among which markers, sFlt-1 to Vasculo-endothelial-Growth-Factor (VEGF) ratio seems to be clinically useful in identifying high risk individuals [17]. After 20^{th} weeks of gestation it is detected by development of hypertension (arterial blood pressure of more than 140/90 mmHg) and proteinuria (>300 mg/liter) in a previously normotensive pregnant woman [3].

Pentoxifylline is a methylxanthine derivative with chemical name of 1-(5-oxohexyl)-3, 7-dimethylxanthine. FDA has approved the agent to treat peripheral arterial disease [18] and it is also shown that pentoxifylline could attenuate inflammatory reactions, reduce ischemia-reperfusion damage, inactivate superoxide anions, improve endothelial function and vasodilatation, reduce viscosity of blood, treat glomerular proteinuric nephropathy and inhibit platelet aggregation [18-21].

Previously it is hypothesized that Pentoxifylline prevents initiation of the disease process, ameliorates symptoms of the disease, prevent progression of preeclampsia toward eclampsia and it could decrease the risk of thrombotic events during and after a preeclamptic gestation and it could explore new horizons in treatment of preeclampsia [9]. In order to evaluate the probable preventive/curative effects of Pentoxifylline on development of preeclampsia, clinical trials should be performed in which the patients should be selected from high risk individuals screened and detected by Doppler ultrasonography of umbilical arteries. The patients should be detected by measurement of

blood pressure and the rate of proteinuria. The drug should be administered to these individuals (400 mg every 12 hours) and included individuals should be followed by Doppler velocimetry of umbilical arteries and sFlt-1 to VEGF ratio [9].

Discussion

Pentoxifylline attenuates Th1-mediated immune reactions [9] and as Th-1-mediated immune responses impair the placentation [11] it is hypothesized that Pentoxifylline improves immune responses to placentation and as it shifts the immune responses toward Th-2 mediated immune responses, it could decrease the risk of initiation of preeclamspsia [9]. Pentoxifylline is an antioxidant and it ameliorates oxidative stress and ischemic damage and improves endothelial function and as oxidative stress and impaired endothelial function are of main culprits of pathogenesis of preeclampsia, it is hypothesized that Pentoxifylline prevents initiation of the disease process and as it could improve maternal/placental circulation it could ameliorate symptoms of the disease [9] and improve outcomes of pregnancy [19]. Pentoxifylline is a vasodilator and reduces vasoconstriction. It also increases flexibility of RBCs and increases RPF, improves renal function and ameliorates proteinuria, in primary glomerular diseases of the kidney [21]. As perfusion and glomerular function of kidneys are impaired during preeclamsia [13], it is hypothesized that Pentoxifylline could improve renal perfusion and function of kidneys and as it could decrease the blood pressure of the patients, it could really unsettle the vicious cycle of the disease [9]. Additionally as Pentoxifylline could ameliorate proteinuria, kidneys do not lose anti-thrombotic proteins [9]. Pentoxifylline also equilibrates the imbalance between prostacyclins and Thromboxanes and it increases production of Plasminogen Activator. It is an anti-coagulant agent and decreases blood coagulability [22,23]. As thrombotic events could shift the preeclampsia toward eclampsia, as an anti-coagulant agent, Pentoxifylline could prevent progression of preeclampsia toward eclampsia and it could also decrease the risk of post-partum thromboembolic events [9].

Conclusion

All clues together, Pentoxifylline could improve immune responses during pregnancy and down-regulate many inflammatory cytokines increased during preeclampsia, reduce ischemia-reperfusion injury, improve endothelial function, enhance vasodilatation and placental circulation, ameliorate proteinuria, inhibit platelet aggregation and increase activity of fibrinolytic enzymes and decrease prostaglandin synthesis and the risk of preterm labor and as it is previously hypothesized Pentoxifylline could prevent and decelerate progression of preeclampsia, as well as severity of its symptoms and it could lift the burden of the disease.

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