行政院國家科學委員會補助專題研究計畫成果報告

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※ 中文：降壓藥物對於子癇前症患者及新生兒血管活性物質之影響 ※

※ 英文：**The effects of antihypertensive treatments to the serum vasoastive** ※

※ **substances** in pre-eclampstic patients and neonates ※

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計畫主持人：林 珍 榮 醫師

共同主持人：

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一、中文摘要

子癇前症是人類懷孕過程中重要併發症之一，形成母親與新生兒的死亡或早產之主要原因。臨床上以蛋白尿及高血壓為徵候，其成因尚未完全明瞭。主要是以血管收縮，以及血管內皮細胞受損為主，導致各器官之血流量減少。由於內皮細胞損傷，呈現血管收縮的現象，使人們推論內皮細胞產生之物質，如內皮素，可能在子癇症之病理上，扮演重要的角色。近年來科學家發現血管內皮細胞分泌的內皮素，實質上調控著血管張力以及局部血流量，且在子癇前症的孕婦中，發現血中內皮素濃度明顯上升，亦暗示著局部內皮細胞受損與內皮素之釋放增加息息相關。除內皮素之外，前列腺素與血栓素，對於子癇前症患者血管活性，亦以有重要關連； 前列腺素 I2 是一強力血管擴張劑，此物質生成之降低，對於子癇前症的臨床表現，具有重要意義。懷孕時，前列腺素 I2 及代謝產物會逐月增加，然而子癇前症病患則明顯下降，生理情況時，前列腺素 I2 可抑制血小板凝集，並維持胎盤血管擴張，如其濃度下降，則不能對抗內皮素，血栓素及升壓物質造成的血管收縮，而形成高血壓。血栓素 A2 亦是懷孕過程中，隨時間逐漸增加的血管活性物質，它可形成血管強力收縮，並與前列腺素 I2 拮抗，在子癇前症患者中，血栓素的增加，合併前列腺素的減少，形成內在血管活性物質(收縮物質 vs. 擴張物質) 失調，可視為此症主要的病理成因。多種降壓藥物皆曾試用於子癇前症患者，新型鈣離子阻斷劑， Nicardipine, 由於血管之選擇性高，故具有良好的降壓效果；且在試管實驗中得知， Nicardipine 可以阻斷內皮素之生成，而內皮素又為子癇前症患者，血中重要的血管收縮物質，故本實驗嘗試應證 Nicardipine 是否有效抑制子癇前症患者內皮素的產生，並控制其血壓，同時以 Nicardipine 與其他降壓藥物，如 Labetalol (阻斷劑)或 Hydralazine (平滑肌擴張劑)，比較它們在子癇前症患者身上降壓效果，亦同時探討不同降壓藥物對於該類患者及新生兒血中之血管活性物質，如內皮素，前列腺素及血栓素之影響；藉不同藥物之治療療效，觀察與血管活性物質濃度的相關性，以明瞭疾病、藥效與作用機轉之關連性。

關鍵詞：子癇前症，內皮素，前列腺素，血栓素，降壓藥

Abstract

Preeclampsia consists of the proteinuria and hypertensive status during the pregnancy, leading to the major cause of maternal and fetal mortality and morbidity. Pathologically, preeclampsia is characterized by vasospasm, reduced blood flow to various organs, and endothelial cell damage. Because endothelial cell injury and vasospasm are the consistent findings in preeclampsia, it is hypothesized that endothelial derived substances such as endothelin may play a central role in the pathophysiology of preeclampsia. There are increasing evidences that the vascular endothelium plays an

important role in the regulation of vessel tone and regional blood flow. Endothelin, a peptide produced and secreted by endothelial cells has been isolated from human endothelial cells. Plasma endothelin levels have been reported to be increased in pre-eclamptic women implying that local endothelial cell injury may be associated with enhanced endothelin release. Other than endothelin, a disturbance of the thromboxane (TX) $A_2(B_2)$ and prostacyclin (PGI_2) balance also supports the hypothesis that endothelial damage may caused by an immune maladaptation and is intimately involved in the pathogenesis of preeclampsia. It has been suggested that defective prostaglandin (PG) production or a loss of response to PGs contributes to the development of pregnancy-induced hypertension. Prostacyclin (PGI_2) is a potent vasodilator, an inhibitor of platelet aggregation, and an inhibitor of uterine contractility. A deficiency in its production during pregnancy would contribute to the clinical manifestation of preeclampsia. Thromboxane (TX) A_2 is a potent vasoconstrictor, a stimulator of platelet aggregation, and a stimulator of uterine contractility. The production of TXA_2 is increased during normal pregnancy because maternal plasma concentration and its stable metabolite, TXB_2, are higher during late pregnancy than during midpregnancy or the nonpregnant state. TXA_2 opposed the action of PGI_2. It occurred to us that the deficiency in PGI_2 production by preeclamptic placenta could be coupled to enhance production of TXA_2 similar to the imbalances in these eicosanoids that have been suggested for the development of pathogenesis of preeclampsia. The ratio of TXB_2/6-keto-$PGF_{1\alpha}$ (metabolite of PGI_2) was significantly elevated in preeclampsia comparing with normotensive pregnancy and demonstrating an imbalance between and vasodilator eicosanoids.

Nicardipine, a new potent calcium entry blocker, exhibited a relatively selective vasodilatory effect to peripheral vessels and was recommended for the antihypertensive treatment in preeclampsia. This L-type calcium channel blocker was also demonstrated to have an antagonistic action to the production of endothelin in endothelial culture cell in vitro. In the present study, we compare nicardipine, with labetalol ($\alpha+\beta$ blocker) and hydralazine (smooth muscle dilator), for the the antihypertensive treatment of preeclamptic patients. Meanwhile, the levels of endogenous vasoactive substances, ET-1, TXB_2 and PGI_2 in both maternal and neonatal serum were assessed, and their clinical correlations to different antihypertensive regimens were evaluated.

Keywords: Pre-eclampsia, endothelin, prostaglandin, thromboxane, antihypertensives.

二、緣由與目的

Preeclampsia is considered one of the most significant health problem in human pregnancy (Dennis et al., 1982; Roberts, 1984). It complicates approximately 5% to 7% of human pregnancies and is one of the major causes of maternal and fetal mortality and morbidity, including fetal growth retardation and premature delivery (Zuspan, 1991). It is primarily characterized by proteinuria (urinary protein > 0.3 gm/day) and increased vasoconstriction, leading to maternal hypertension (systemic arterial BP ≥ 140/90 mm Hg) and reduced uteroplacental flow. The etiology of preeclampsia remains unclear. One of its cardinal features is an abnormal increase in peripheral vessel resistance, suggesting the possible etiology involvement of vasoconstrictive humoral factors. Endothelin-1 (ET-1) is a potent vasoconstrictor and has been suggested to be involved in the development of the pathophysiology of preeclampsia (Yanagisawa et al., 1988; Ihara et al., 1991;

Tsunoda et al., 1992). Concentrations of ET-1 in the plasma of healthy pregnant women at various gestational ages were not different from that of nonpregnant women (Ihara et al.,1991; Tsunoda et al., 1992). While in the neonates, ET-1 levels in the plasma of umbilical artery and vein were three times higher than that in the maternal plasma (Ihara et al., 1991; Buemi et al., 1994). Higher levels of ET-1 were found in the plasma of pregnant women with preeclampsia, especially in the women with severe preeclampsia when compared with the reduced values of the pregnant women without hypertension, and this increase in ET-1 was considerable (Florijn et al., 1991; Tsunoda et al., 1992). The plasma endothelin concentration was 150% higher in the women with preeclampsia than in the nonhypertensive pregnant women. It decreased to normal levels with the fall in blood pressure following delivery, suggesting an interaction between the endothelin and preeclampsia which were consistent with the findings of other investigator (Tsunoda et al., 1992; Taylor et al., 1990). McMahon and colleagues speculated that increased local production of endothelin in the placenta may contribute to the placental vascular insufficiency and fetal growth retardation seen in preeclampsia (McMahon et al., 1993).

Meanwhile, preeclampsia is frequently associated with endothelial cell damage and disseminated intravascular coagulation (Altcheck et al., 1968; Redman et al., 1977; Wallenburg, 1987). This caused the other mechanisms for the increased vascular responsiveness in pre-eclampsia to be considered. It has been suggested that defective prostaglandin (PG) production or a loss of response to PGs contributes to the development of pregnancy-induced hypertension (Dennis et al., 1982; Everett et al., 1978). Prostacyclin (PGI_2) is a potent vasodilator, an inhibitor of platelet aggregation, and an inhibitor of uterine contractility (Moncada, 1979; Omini, 1979). A deficiency in its production during pregnancy would contribute to the clinical manifestation of preeclampsia. During normal pregnancy, the production of PGI_2 is increased, because maternal plasma concentration of its stable metabolite, 6-keto $PGF_{1\alpha}$, as well as its urinary metabolites, are higher during late pregnancy than during early pregnancy or the nonpregnant state (Goodman, 1982). A considerable amount of data indicates that PGI_2 production is decreased in umbilical arteries, placental veins, uterine vessels, and subcutaneous vessels obtained from preeclamptic women as compared with normally pregnant women (Remuzzi et al., 1980; Bussolino et al., 1980; Downing et al., 1980). The significance of PGI_2 produced should not be underestimated. The potential role of PGI_2 is to inhibit platelet aggregation and maintain placental vascular vasodilatation. With less being produced in preeclampsia, the vasoconstrictor effects of endothelins, thromboxane, and catecholamines would not be efficiently opposed, leading to hypertension.

The production of thromboxane (TX) A_2 is also increased during normal pregnancy because maternal plasma concentration and its stable metabolite, TXB_2, are higher during late pregnancy than during midpregnancy or the nonpregnant state (Mitchell et al., 1978; Ylikorkala et al., 1980). TXA_2 opposed the action of PGI_2. TXA_2 is a potent vasoconstrictor, a stimulator of platelet aggregation, and a stimulator of uterine contractility (Moncada et al., 1979; Wilhelmsson et al., 1981). It occurred to us that the deficiency in PGI_2 production by preeclamptic placenta could be coupled to enhance production of TXA_2 similar to the imbalances in these eicosanoids that have been suggested for the development of pathogenesis of preeclampsia.

Considering the antihypertensive treatment for the preeclampsia, calcium channel blockers have potential advantages over other drugs in the treatment of hypertension, particular during pregnancy: they cause vasorelaxation and lower peripheral vascular resistance, diminished vascular sensitivity to vasopressive hormones such as angiotensin II, and decreased platelet

aggregation (Fiéet et al., 1992). Nicardipine, another dihydropyridine derivative, is a potent antihypertensive drug acting more selectively on vessels than on the myocardium, lesser negative inotropic effect and less reflex tachycardia (Wallin et al., 1988). Recently it has been applied for the treatment of hypertension during pregnancy due to its effectiveness as well as its pharmacological in vitro antagonism to the endothelin which acts as one of the important vasoactive substances in the pathogenesis of pre-eclamptsia (Carbonne et al., 1993; Haynes et al., 1993). Within the cell culture, nicardipine could antagonize the production of endothelin which implies the potential antagonism of this L-type calcium channel blocker with the potent endogenous vasoconstrictor (Haynes et al., 1993). While the in vivo effect of nicardipine to the serum vasoactive substances, such as ET-1, PGI_2 and TXB_2, of preeclamptic patients remains to be verified. So we present this project to study the in vivo effect of nicardipine in the treatment of preeclamsia as well as evaluating the interactions between these antihypertensive drugs and serum vasoactive substances before and after delivery.

三、結果與討論

結果部份

1. 本計畫申請金額為 100 萬，核定為 40 萬。實驗組與對照組各 20 名病人，分別為正常孕婦與子癇前症孕婦，對給藥(Nicardipine)前後(15 天後)及產後，分別測定血中 ET-1,PGI_2 及 TXB_2 濃度並比較之。

顯示結果：

a. 子癇前症病人於治療前，血中 ET-1 濃度高於對照組($p<0.01$)。
b. 子癇前症病人於治療前，血中 TXB_2 濃度略高於對照組，但統計上無差異性，而 PGI_2 則無差別。
c. 使用 Nicardipine 後，子癇前症患者血中 ET-1 下降，但仍高於對照組，直至產後降至與對照組相近。
d. 使用 Nicardipine 組，血中 PGI_2 與 TXB_2 對照組無統計上差異。

討論部份

1. 子癇前症患者於治療前血中 ET-1 高於對照組，說明其血管收縮狀態及其病因。
2. 至於血中 TXB_2 濃度高於對照組，則另一血管收縮之佐證，而 PGI_2 卻無明顯差距，表示血管擴張物質在此並無重要角色。
3. 使用 L-type 鈣離子阻斷劑 Nicardipine，的確可以拮抗 EF-1 之生成，並產生降壓效果，但無法拮抗其他成因路徑。

四、計畫成果自評

1. 計畫經費不足以完成整個計畫，應分年執行。
2. 研究成果於臨床醫學有應用價值，且對基礎醫學病因基轉有進一步的認識。
3. 病人數目仍嫌不足，有待進一層之探討。

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