นิพนธ์ต้นฉบับ

# Therapeutic comparison between vasodilators and conventional therapy in severe form of nephrosis associated with focal segmental glomerulosclerosis.

Prasit Futrakul *
Makumbrong Poshyachinda ** Narisa Futrakul ***
Tawatchai Chaiwatanarat Rajanee Sensiriwatana *
Dhevy Watana * Pornchai Kingwatanakul *

**Futrakul P, Poshyachinda M, Futrakul N, Chaiwatanarat T, Sensiriwatana R, Watana D, Kingwatanakul P. Therapeutic comparison between vasodilators and conventional therapy in severe form of nephrosis associated with focal segmental glomerulosclerosis. Chula Med J 1993 Nov ; 37(11) : 673-678**

*14 nephrotics associated with FSGS clinically classified as severe were subjected to intrarenal hemodynamic assessment. The intrarenal hemodynamics characteristic of severe FSGS were as follows.*

*(1) marked elevation of afferent and efferent arteriolar resistances; RA or RE above 10,000 dyne.s.cm $^{-5}$ (normal 2000-2600 dyne.s.cm $^{-5}$ )*

*(2) more than 50 percent reduction of ultrafiltration coefficient; KFG less than 0.03 ml/sec/mmHg (normal 0.06 ml/sec/mmHg)*

*(3) more than 50 percent reduction of renal plasma flow; RPF less than 250 ml/min/1.73 m $^{2}$ (normal 500-660 ml/min/1.73 m $^{2}$ )*

*(4) more than 50 percent reduction of glomerular filtration rate; GFR less than 50 ml/min/1.73 m $^{2}$ (normal 100-120 ml/min/1.73 m $^{2}$*

*(5) intraglomerular capillary hypertension; PG more than 55 mmHg (normal 47-54 mmHg)*

*Therapeutic comparison between the 8 conventionally-treated (prednisolone + cyclophosphamide) and 6 vasodilator-treated (antiplatelet + calcium channel blocker + angiotensin converting enzyme inhibitor) revealed that all in the former developed end-stage renal disease and deceased whereas all in the later showed progressive clinical improvement and survived.*

**Key words** : *Nephrosis, Focal segmental glomerulosclerosis, Vasodilators, Hemodynamics.*

Reprint request : Futrakul P, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. October 1, 1993.

* Department of Pediatrics, Faculty of Medicine, Chulalongkorn University.

** Department of Radiology, Faculty of Medicine, Chulalongkorn University.

*** Department of Medicine, Faculty of Medicine, Mahidol University.

**ประสิทธิ์ ฟูตระกูล, มาคุ้มครอง โปษยะจินดา, นริสา ฟูตระกูล, ธวัชชัย ชัยวัฒนะรัตน์, รัชนี เซ็นศิริวัฒนา, เทวี วัฒนา, พรชัย กิ่งวัฒนกุล. การรักษาเปรียบเทียบผู้ป่วยเนฟโฟรสิสโฟกัลเสกเมนตัล โกลเมอรูโลสเกอโรสิสชนิดรุนแรง ระหว่างวิธีใช้ฤทธิ์ขยายหลอดเลือดกับวิธีสากลนิยม. จุฬาลงกรณ์เวชสาร 2536 พฤศจิกายน ; 37(11) : 673-678**

*ผู้ป่วยเนฟโฟรสิสชนิดโฟกัลเสกเมนตัล โกลเมอรูโลสเกอโรสิสที่มีอาการทางคลินิกรุนแรง จำนวน 14 ราย ได้รับการตรวจทางโลหิตพลศาสตร์ของไต ซึ่งพบความผิดปกติสำคัญคือ (1) ความต้านทานผนังหลอดเลือดเข้าและออกโกลเมอรูลัส (afferent and efferent arteriolar resistances) มากกว่า 10,000 ดายน์. วินาที. ซม.* $^{-5}$ *(2) ค่าสัมประสิทธิ์การกรองพลาสมาของโกสเมอรูลัส (ultrafiltration coefficeient of glomerular capillary) ลดต่ำกว่า 50 เปอร์เซ็นต์ (3) อัตรากรองพลาสมาของโกลเมอรูลัสลดต่ำกว่า 50 เปอร์เซ็นต์ (4) ปริมาณเลือดหล่อเลี้ยงไตลดต่ำกว่า 50 เปอร์เซ็นต์ (5) ความดันภายในหลอดเลือดฝอยโกลเมอรูลัสสูงกว่าปกติ*

*การเปรียบวิธีรักษาด้วยยาฤทธิ์ขยายหลอดเลือด (6 ราย) กับวิธีสากลนิยม (8 ราย) พบว่า วิธีรักษาด้วยยาฤทธิ์ขยายหลอดเลือดได้ผลดีในทั้ง 6 ราย โดยมีการทำงานของไตต่าง ๆ ดีขึ้น เทียบกับผู้ป่วยทั้ง 8 รายที่รักษาโดยวิธีสากลนิยม ซึ่งต่างเข้าสู่ภาวะไตวายขั้นสุดท้ายและตาย*

The long-term prognosis of nephrosis (NS) associated with focal segmental glomerulosclerosis (FSGS) had long been considered to be unfavourable, clinically steriod-resistant and commonly destined for chronic renal insufficiency (5 years survival 50 percent). [1-2] However, recent improvement (80-90 percent) in clinical outcome and better acturial-survival-rate in the FSGS nephrotics with particular notion to those associated with normal or mild impairment of creatinine clearance, may simply implicate that there are 2 forms of NS associated with FSGS namely the mild and severe subgroup. [3] Thus, the former manifests clinically with mild hypertension, no anemia, normal or mild renal functional impairment, has partial or total responsiveness to high dose steroid and immunosuppressant and usually shows a slow clinical progression over a prolonged period of time. The latter form is characterized by the severe clinical mainfestation such as moderate to severe hypertension, anemia, severe renal functional impairments and is usually destined for end-stage renal-disease. Therefore, it is our purposes (1) to perform the intrarenal hemodynamic assessment in the severe form of nephrotics with FSGS and (2) to compare the treatment between the conventionally treated (prednisolone + cyclophosphamide) and the vasodilator-treated group (dipyridamole + calcium channel blocker +angiotensin converting enzyme inhibitor).

## Material and Method

Fourteen cases of severe form of nephrosis (NS) associated with focal segmental glomerulosclerosis (FSGS) were subjected to intrarenal hemodynamic assessment as described in detail elsewhere. [4-5] The clinical identification of severity is characterized by the presence of hypertension, moderate to severe degree of renal functional impairment, severe degree of tubular transporting defect and the progressive deterioration of clinical status. [4-5] These 14 NS were further subdivided into 2 groups according to the type of therapeutic intervention; eight were placed on conventional therapy consisting of prednisolone 1-2 mg/kg/day and cyclophosphamide 1-2 mg/kg/day, 6 were supplemented with vasodilators (a combination of dipyridamole 10-15 mg/kg/day + calcium channel blockers, nefidipine 0.5-2 mg/kg/day or isradipine 2.5-10 mg/day + angiotensin converting enzyme inhibitor; enalapril 0.5-2 mg/kg/day or cilazapril 2.5-10 mg/day).

Therapeutic endpoint in the vasodilator-treated group has been aimed to achieve the maximal restoration of renal functions in terms of glomerular, tubular and intrarenal hemodynamic subcategories. This form of therapeutic approach has been continuously sustained until the maximal therapeutic response has been accomplished and then continued further of such treatment for a minimum of 1 year. Careful observation and reassessments of all of these corresponding renal functions are mandatary.

Assessment of the therapeutic response of either group had been accomplished by mean of assessing the final clinical outcome, the number of death and the subsequent determination of intrarenal hemodynamics which could be accomplished in 5 patients in the vasodilator treated and in 1 patient in the conventionally-treated group.

## Results

As depicted in Table 1, intraglomerular capillary hypertension (PG above 55 mmHg) was detected in 12 out of 14; the remaining two whose PG were 51 and 53 mmHg respectively had very low serum albumin (0.9 gm% and 1.4 gm%) which might account for the low PG value, according to the method of calculation. A marked increase in renal arteriolar resistance in conjunction with severe reduction of renal plasma flow (RPF), of ultrafiltration coefficient of the glomerular capillary (KFG) and of glomerular filtration rate (GFR) were substantiated in all of them.

**Table 1.** The initial assessment of intrarenal hemodynamics.

| | severe FSGS (Control) n = 8 | severe FSGS (Vasodilators) n = 6 | 2-Tail Probability | P value |
|---|---|---|---|---|
| Intraglomerular hydrostatic pressure (PG) mmHg | 55 ± 2 | 57 ± 3 | 0.366 | NS |
| Afferent arteriolar resistance (RA) dyne.s.cm $^{-5}$ | 19181 ± 10246 | 18357 ± 14808 | 0.904 | NS |
| Efferent arteriolar resistance (RE) dyne.s.cm $^{-5}$ | 14844 ± 7165 | 14489 ± 9962 | 0.939 | NS |
| Ultrafiltration coefficient (KFG) ml/sec/mmHg | 0.02 ± 0.01 | 0.014 ± 0.01 | 0.138 | NS |
| Renal plasma flow (RPF) ml/min/1.73 m $^{2}$ | 248 ± 134 | .150 ± 66 | 0.096 | NS |
| Glomerular filtration rate (GFR) ml/min/1.73 m $^{2}$ | 42 ± 17 | 33 ± 4 | 0.187 | NS |

After 5 years of follow-up, 8 out of 8 nephrotics in the conventionally-treated were all deceased, whereas 6 of the vasodilator treated were all survived with progressive improvement in renal function.

**Table 2.** Follow-up intrarenal hemodynamic assessment.

| | PG | RA | RE | KFG | GFR | RPF | PTCB |
|---|---|---|---|---|---|---|---|
| **I Vasodilator group** | | | | | | | |
| **I** | **56** | **14092** | **20370** | **0.01** | **31** | **100** | **69** |
| A | 51 | 5205 | 6249 | 0.02 | 36 | 153 | 117 |
| **I** | **61** | **16383** | **15906** | **0.01** | **33** | **92** | **59** |
| A | 53 | 1776 | 3748 | 0.03 | 61 | 291 | 230 |
| **I** | **57** | **10965** | **5136** | **0.017** | **40** | **199** | **159** |
| A | 52 | 2039 | 2510 | 0.05 | 95 | 414 | 319 |
| **I** | **56** | **14579** | **12073** | **0.01** | **28** | **116** | **88** |
| A | 52 | 2303 | 3269 | 0.05 | 106 | 337 | 231 |
| **I** | **55** | **14173** | **10023** | **0.013** | **32** | **250** | **218** |
| A | 53 | 1317 | 1328 | 0.04 | 73 | 444 | 371 |
| **II Conventional group** | | | | | | | |
| **I** | **55** | **9017** | **7699** | **0.029** | **71** | **483** | **412** |
| A | 59 | 51223 | 33200 | 0.013 | 31 | 89 | 58 |

I = initial value

A = after-treatment value

## Discussion

The clinical course of these 14 steroid-resistant nephrotics associated with FSGS confirmed that the overall prognosis of this disease is generally unfavourable among those treated conventionally with prednisolone and immunosuppressive agent. Progressive deterioration of renal function and development of end-stage-renal disease had been well substantiated in all of these 8 patients so-treated. In contrast, a sustained and progressive improvement in renal functions namely an increase in creatinine clearance, a decrease in amount of proteinuria, reduction of hypertension and a 100 percent survival has been accomplished only by therapy with vasodilators. Such therapeutic benefit with vasodilators may plausibly be explained by the intrarenal hemodynamic abnormality observed prior to the treatment and by the subsequent change following the correction of such hemodynamic alteration with vasodilators.

Marked reduction of renal plasma flow had been consistently observed in these nephrotics with FSGS.[4-7] Increased intrarenal resistance had been confirmed by the elevated afferent and efferent arteriolar resistances, which might be responsible for the reduction of renal plasma flow.

Enhanced intrarenal resistance could be explained by the demonstration of elevated level of thromboxane B2 and of relatively decreased production of prostacyclin during the nephrotic state.[8-9] Nevertheless, there are empirical evidences that other vasoconstrictive mediators known to be aggravated in the severe form of NS such as endothelin, angiotensin II and eicosanoid products may also share their roles in the enhancement of intrarenal resistance.[10-13]

The vasoconstrictive effect of these modiators in the presence of glomerular endothelial dysfunction with defective production of vasodilator such as prostacyclin would increase the afferent, efferent arteriolar resistances and contraction of the mesangial cell by which it would reduce the renal plasma flow, glomerular filtration rate and ultrafiltration coefficient of the glomerular capillary.

The increased intraglomerular capillary hydrostatic pressure is likely to be due to the marked reduction of ultrafiltration coefficient of the glomerular capillary and to the preponderant constriction of the efferent arteriole.

The reduction of renal plasma flow may have a significant impact upon the hemorrheology in the renal microcirculation. Impedement of blood flow in the renal microcirculatory level has also been influenced by the hypercoagulability and hyperviscosity of blood, platelet hyperaggregate, defective deformability of the red blood cell and the local intravascular fibrin formation in the glomerular capillary.[14-17] Sustained shortenning of platelet half-life was observed in NS with FSGS.[14-15]

In accord with the preceding concept of hypoperfusion secondary to the glomerular endothelial dysfunction, therapeutic intervention with combined vasodilators yielded a beneficial outcome. Reduction of intrarenal resistances improved the RPF, GFR, KFG as well as reduced PG. Combined usage of vasodilators is likely to operate with maximal efficacy in such provasoconstrictive state of the renal microcirculation induced by multiple vasoconstrictors. Such therapeutic benefit is quite contrast to the result obtained in the 8 conventionally treated nephrotics who all ended up with end-stage renal-disease and deceased. Progressive increase in intrarenal resistance, intraglomerular capillary hypertension and in reciprocal reduction of RPF in the conventionally treated nephrotics. This would render a supportive evidence to the beneficial role of vasodilators in correction of the glomerular endothelial dysfunction.

## References

1. Cameron JS, Turner DR, Ogg CS, Chantler C, Williams DG. The longterm prognosis of patients with focal segmental glomerulosclerosis. Clin Nephrol 1978 Dec; 10(6) : 213-18
2. Banfi G, Moriggi M, Sabadini E, Fellis G, Dû Amico G, Ponticelli C. The impact of prolonged immunosuppression on the outcome of idiopathic focal segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study. Clin Nephrol 1991 Aug; 36(2) : 53-9
3. Korbet SM. The treatment of focal segmental glomerular sclerosis : steroid-resistance or steroid-reluctance? Kidney : A current survery of world literature 1992; 1 : 2-3.
4. Kimura G, Deguchi F, Kojima S, Ashida T, Yoshimi H, Abe H, Kawano Y, Yoshida K. Effect of a calcium entry blocker, nicardipine on intrarenal hemodynamics in essential hypertension. Am J Kidney Dis 1991 Jan; 17(1) : 47-54
5. Futrakul P, Poshyachinda M, Futrakul N, et al. Intrarenal hemodynamics alterations and tubular functions in nephrotic syndrome associated with focal segmental glomerulosclerosis (FSGS) : a pathogenetic and therapeutic implication. In : Andreucci VE, Dal Canton A, eds. Current Therapy in Nephrology. Milano : Wichtig Editore, 1993 : 107-14

6. Scandling JD, Black VM, Deen WM, Meyers BD. Glomerular permselectivity in healthy and nephrotic humans. Adv Nephrol 1992; 21 : 159-75

7. Futrakul P, Thamaree S, Watana D. Severely depleted renal plasma flow and enhanced renal vascular resistance in severe form of glomerulonephritis : a therapeutic benefit with vasodilators. J Am Soc Nephrol 1992; 3 : 561

8. Futrakul P, Futrakul N. Nephrotic syndrome. In : Futrakul P,ed. Clinical Nephrology, Bangkok: Chulalongkorn University Press, 1993 : 66-106

9. Thamaree S, Poshyachinda M, Futrakul N, et al. Elevated TXB2 and altered intrarenal hemodynamics in nephrotic patients-a therapeutic implication with combined platelet aggregation inhibitor, calcium channel blocker and ACE inhibitor. Proceedings 8 th International Conference on Prostaglandins and Related Compounds, Montreal, 1992 : 63

10. Remuzzi G, Fitz Gerald GA, Patrono C. Thromboxane synthesis and action within the kidney. Kidney Int 1992 Jun; 41(6) : 1483-93

11. Rosivall L, Tangner R, Navar LG. Intrarenal formation of angiotensin II and its effect on renal hemodynamics. In : Davison AM, ed. Nephrology I, London : Bailliere Tindall, W.B. Saunders, 1988. 46-56.

12. Ichikawa I. Harris RC. Angiotensin action in the kidney : renewed insight into the old hormone. Kidney Int 1991 Oct; 40(4) : 583-96

13. Ohta K, Hirata Y, Shichiri M, Kanno K, Emori T, Tomita K, Marumo F. Urinary excretion of endothe-lin-1 in normal subjects and patients with renal disease. Kidney Int 1991 Feb; 39(2) : 307-11

14. Futrakul P, Poshyachinda M, Mitrakul C. Focal sclerosing glomerulonephritis : a kinetic evaluation of hemostasis and the effect of anticoagulant therapy : a controlled study. Clin Nephrol 1978 Nov; 10(5) : 180-6

15. Futrakul P, Poshyachinda M, Mitrakul C. Hypercoagulability in the nephrotic syndrome : use of anticoagulation. Proceedings VIII th International Congress of Nephrology, Athens, 1981: 297-301

16. Strauss J, Zilleruelo G, Freundlich M, Abitol C. Less commonly recognized features of childhood nephrotic syndrome. Pediatr Clin North Am 1987 Jun; 34(3) : 591-607

17. Cecchin E, De Marchi S, Panarello G, De Angelis V. Rheological abnormalities of erythrocyte deformability and increased glycosylation of hemoglobin in the nephrotic syndrome. Am J Nephrol 1987; 7(1) : 18-21