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 *


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⁻¹ (normal 2000-2600 dyne.s.cm⁻¹)
(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 m² (normal 500-660 ml/min/1.73 m²)
(4) more than 50 percent reduction of glomerular filtration rate; GFR less than 50 ml/min/1.73 m² (normal 100-120 ml/min/1.73 m²)
(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.
ผู้ปรับเปลี่ยนฟิสิกซ์สินิตร扶贫工作สัมผัสผิวภายนอก โลกลมอุรุโภคลอมอุรุสตีมีการทางกลมอุรุสตีผ่านจนกว่า 14 ราย ได้รับการตรวจทางโลหิตเฉพาะสาหร่ายของไอ ซึ่งพบความผิดปกติสำคัญคือ (1) ความเสื่อมหวานในหลอดเลือดขับและออกโลกลมอุรุสตี (afferent and efferent arteriolar resistances) มากกว่า 10,000 ตำมี. นิวม. ฯ (2) คำนวณประสิทธิ์การกรองพลาสมาของโลกลมอุรุสตี (ultrafiltration coefficient of glomerular capillary) ลดต่ำกว่า 50 เบอร์ชั้นค์ (3) อัตราการผ่านพลาสมาของโลกลมอุรุสตีลดต่ำกว่า 50 เบอร์ชั้นค์ (4) ปริมาณหลอดเลือดยังคงลดต่ำกว่า 50 เบอร์ชั้นค์ (5) ความเหลื่อมไทในหลอดเลือดฝอยโลกลมอุรุสตีผิดปกติ

การปรับเปลี่ยนฟิสิกซ์สินิตร้าฮุชิชาย่อมหลอดเลือด (6 ราย) ทั้งหมดสำนึกหนึ่ง (6 ราย) พบว่า ให้รักษาด้วยยาฮุชิชาย่อมหลอดเลือดได้ผลดีในหลัก 6 ราย โดยมีการรายงานว่าผู้ต่าง ๆ ดีขึ้น เห็นผลก่อนผู้ป่วยทั้ง 6 รายที่รักษาได้รักษาสำนึกหนึ่งดีขึ้นสุขภาพดีและหาย
The long-term prognosis of nephrosis (NS) associated with focal segmental glomerulosclerosis (FSGS) had long been considered to be unfavourable, clinically steroid-resistant and commonly destined for chronic renal insufficiency (5 years survival 50 percent). However, recent improvement (80-90 percent) in clinical outcome and better actuarial-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. 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 manifestation 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. 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. 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 mandatory.

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 (KPG) and of glomerular filtration rate (GFR) were substantiated in all of them.
Table 1. The initial assessment of intrarenal hemodynamics.

<table>
<thead>
<tr>
<th></th>
<th>Severe FSGS (Control)</th>
<th>Severe FSGS (Vasodilators)</th>
<th>2-Tail Probability</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraglomerular hydrostatic pressure (PG) mmHg</td>
<td>55 ± 2</td>
<td>57 ± 3</td>
<td>0.366</td>
<td>NS</td>
</tr>
<tr>
<td>Afferent arteriolar resistance (RA) dyne.s.cm⁻¹</td>
<td>19181 ± 10246</td>
<td>18357 ± 14808</td>
<td>0.904</td>
<td>NS</td>
</tr>
<tr>
<td>Efferent arteriolar resistance (RE) dyne.s.cm⁻¹</td>
<td>14844 ± 7165</td>
<td>14489 ± 9962</td>
<td>0.939</td>
<td>NS</td>
</tr>
<tr>
<td>Ultrafiltration coefficient (KFG) ml/sec/mmHg</td>
<td>0.02 ± 0.01</td>
<td>0.014 ± 0.01</td>
<td>0.138</td>
<td>NS</td>
</tr>
<tr>
<td>Renal plasma flow (RPF) ml/min/1.73 m²</td>
<td>248 ± 134</td>
<td>150 ± 66</td>
<td>0.096</td>
<td>NS</td>
</tr>
<tr>
<td>Glomerular filtration rate (GFR) ml/min/1.73 m²</td>
<td>42 ± 17</td>
<td>33 ± 4</td>
<td>0.187</td>
<td>NS</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>I Vasodilator group</th>
<th>PG</th>
<th>RA</th>
<th>RE</th>
<th>KFG</th>
<th>GFR</th>
<th>RPF</th>
<th>PTCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>56</td>
<td>14092</td>
<td>20370</td>
<td>0.01</td>
<td>31</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>A</td>
<td>51</td>
<td>5205</td>
<td>6249</td>
<td>0.02</td>
<td>36</td>
<td>153</td>
<td>117</td>
</tr>
<tr>
<td>I</td>
<td>61</td>
<td>16383</td>
<td>15906</td>
<td>0.01</td>
<td>33</td>
<td>92</td>
<td>59</td>
</tr>
<tr>
<td>A</td>
<td>53</td>
<td>1776</td>
<td>3748</td>
<td>0.03</td>
<td>61</td>
<td>291</td>
<td>230</td>
</tr>
<tr>
<td>I</td>
<td>57</td>
<td>10965</td>
<td>5136</td>
<td>0.017</td>
<td>40</td>
<td>199</td>
<td>159</td>
</tr>
<tr>
<td>A</td>
<td>52</td>
<td>2039</td>
<td>2510</td>
<td>0.05</td>
<td>95</td>
<td>414</td>
<td>319</td>
</tr>
<tr>
<td>I</td>
<td>56</td>
<td>14579</td>
<td>12073</td>
<td>0.01</td>
<td>28</td>
<td>116</td>
<td>88</td>
</tr>
<tr>
<td>A</td>
<td>52</td>
<td>2303</td>
<td>3269</td>
<td>0.05</td>
<td>106</td>
<td>337</td>
<td>231</td>
</tr>
<tr>
<td>I</td>
<td>55</td>
<td>14173</td>
<td>10023</td>
<td>0.013</td>
<td>32</td>
<td>250</td>
<td>218</td>
</tr>
<tr>
<td>A</td>
<td>53</td>
<td>1317</td>
<td>1328</td>
<td>0.04</td>
<td>73</td>
<td>444</td>
<td>371</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II Conventional group</th>
<th>PG</th>
<th>RA</th>
<th>RE</th>
<th>KFG</th>
<th>GFR</th>
<th>RPF</th>
<th>PTCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>55</td>
<td>9017</td>
<td>7699</td>
<td>0.029</td>
<td>71</td>
<td>483</td>
<td>412</td>
</tr>
<tr>
<td>A</td>
<td>59</td>
<td>51223</td>
<td>33200</td>
<td>0.013</td>
<td>31</td>
<td>89</td>
<td>58</td>
</tr>
</tbody>
</table>

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. 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. 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.

The vasoconstrictive effect of these mediators 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 hemorrhology 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 hyperaggregates, defective deformability of the red blood cell and the local intravascular fibrin formation in the glomerular capillary. Sustained shortening of platelet half-life was observed in NS with FSGS.

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


