Efficacy and Safety of Valsartan As an Antiproteinuric Agent in Children Aged 3 to 18 Years with Minimal Change Nephrotic Syndrome

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ABSTRACT:

BACKGROUND:

Nephrotic syndrome is primarily a pediatric disorder which causes heavy proteinuria , hypoalbuminemia , edema, and hyperlipidemia. Most children (90%) with nephrotic syndrome have idiopathic nephrotic syndrome caused in 85% of the patients by minimal change glomerular disease.

Valsartan is an angiotensin II receptor blocker approved in adults for the treatment of hypertension, heart failure and it may also reduce proteinuria in nephritic syndrome.

OBJECTIVE:

The aims of this study are to assess antiproteinuric effect of valsartan in nephrotic syndrome in comparison with propranolol and captopril , and to assess safety of valsartan in pediatric age.

PATIENTS AND METHODS:

A case control study was done for 104 patients who attended three pediatric hospitals (The Central Pediatric Hospital, Al- Elwyia Pediatric Hospital and Ibn Al-Baladi Hospital) where they were newly diagnosed with minimal change nephrotic syndrome and 38 of them (36.5%) were diagnosed with hypertension from 2006 to 2013 and they were followed up for six months (course of disease treatment). Data collected in this study included: age, sex, time of diagnosis and blood pressure was measured. Laboratory tests were done which include: measurement of blood urea, serum creatinine, serum potassium , serum cholesterol, serum albumin, hemoglobin level, liver enzymes (serum glutamate pyruvate transaminase, serum glutamic-oxaloacetic transaminase and serum alkaline phosphatase) and albumin in urine.

RESULT:

Despite comparable reduction in blood pressure among the 3 groups, angiotensin receptor blocker-treated group showed statistically more significant reduction in proteinuria (amount and onset after initiation of therapy) than other groups.

Drug-related adverse events were minor and infrequent, no patient developed dangerous increase in serum potassium, renal function and liver function parameters nor dangerous decrease in mean hemoglobin level.

CONCLUSION:

Valsartan is an effective and safe drug to be used in childhood minimal chang nephrotic syndrom with rapid and consistent antiproteinuric effect even beyond its antihypertensive effect.

KEY WORDS: children,nephritic syndrome,valsartan.

INTRODUCTION:

Nephrotic syndrome is primarily a pediatric disorder and is 15 times more common in children than adults. The incidence is 2-3/100,000 children per year, and the vast majority of affected children will have steroid-sensitive minimal change disease. The characteristic features of nephrotic syndrome are heavy proteinuria (>3.5 g/24 hr in adults or 40 mg/m^2/hr in children), hypoalbuminemia (<2.5 g/dL), edema, and hyperlipidemia[1]. The primary pathology was increased in permeability of the glomerular capillary wall[2]. Most children (90%) with nephrotic syndrome have idiopathic nephrotic syndrome and 85% of patients with idiopathic nephrotic syndrome have minimal change disease.. The remaining 10% of children

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with nephrotic syndrome have secondary nephrotic syndrome[1]. First choice in treatment of nephrotic syndrome is steroid[3].

As a pediatric nephrologists, decreasing the proteinuria as rapidly as possible and as effective as possible is a major aim in minimal change nephrotic syndrome (MCNS) as prolonged proteinuria acts in a dynamic way to mediate the progression of renal disease through interstitial fibrosis as it may stimulate the production of extracellular matrix proteins such as fibronectin, and the profibrotic chemokines MCP-1 (monocyte chemotactic protein 1) and RANTES (regulated on activation normal T-cell expressed and secreted), in addition to activating mitogenic pathways [4].

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers reduce protein excretion by approximately 35% to 40% which is greater than other anti-hypertensive agents, even when the effect of blood pressure reduction on urinary protein excretion has been taken into account. Calcium-channel blockers,on other hand, have variable effect. The nondihydropyridine agents, such as verapamil and diltiazem, have significant antiproteinuric effects in diabetic-but not nondiabetic- kidney disease. The dihydropyridine agents, such as amlodipine and nifedipine, generally have no consistent effect on proteinurea. Other agents, including diuretics and B-blockers have not been shown to have a consistently significant effect on proteinuria [5].

Valsartan is an angiotensin II receptor blocker approved in adults for the treatment of hypertension, heart failure, and left ventricular failure or left ventricular dysfunction in postmyocardial infarction [6]. It's effects primarily result from selective blockade of the angiotensin type II receptor in vascular smooth muscle and adrenal gland[7].http://hyper.ahajournals.org/cgi/content/full/52/2/222 - R7-111054 Beside antihypertensive effect, Valsartan may also reduce proteinuria and have other beneficial effects in patients with underlying kidney disease[8].

The experimental evidence demonstrates that angiotensin receptor blockers (ARBs) possess an anti-inflammatory potential, which might contribute to reducing proteinuria and providing renoprotection[8].

Valsartan effectively lowers blood pressure in children aged 1 to 5 years with hypertension, researchers report [9].In particular, valsartan had no demonstrable negative effects on linear growth, annual weight gain, or progression of head circumference which is a key indicator of brain growth in young children[9].

AIMS OF STUDY:

The aims of this study are to assess antiproteinuric effect and safety of valsartan in nephrotic syndrome in comparison with propranolol and captopril in pediatric age.

PATIENTS AND METHODS:

Two hundred seventeen nephrotic patients were attending 3 pediatric hospitals (The Central Pediatric Hospital, Al- Elwyia Pediatric Hospital and Ibn Al-Baladi Hospital) between 2006 to 2013. One hundred four patients were selected and subjected to this study according to the following criteria (inclusion criteria):

1. Newly diagnosed nephrotic syndrome with verbal acceptance of the patient's parents after full explanation of the study goals, interventions and hazards including performing percutaneous renal biopsy.

2. For children aged 3 to 8 years old, characteristic triad manifestations of nephrotic syndrome (i.e. generalized body edema, nephrotic range proteinuria, hypoproteinemia) with neither active sediment nor significant hematuria in the general urine exam, normal renal function tests, normal genitourinary tract ultrasonic exam, negative hepatitis B and C serology, normal C3 and C4 complement level, and if any of these investigations array showed abnormality, percutaneous renal biopsy showing MCNS.

3. For all children older than 8 years, besides the criteria of younger children but only whose renal biopsy had showed MCNS.

4. Patients with high blood pressure with percutaneous renal biopsy showing MCNS.

Exclusion criteria:

1. Patients younger than 3 years of age because of the difficulty to swallow the Valsartan (Diovan, Novartis) tablet.

2. Calculated creatinine clearance <30 mL/min per 1.73 m^2.

3. Serum potassium more than the upper limit of the reference range.

4. Ultrasonic manifestation of unilateral renal artery stenosis i.e. differences between the 2 kidneys sizes more than 10% or reflux nephropathy.

5. Positive serology for hepatitis B or C.

6. If renal biopsy showing primary disease other than minimal change nephritic syndrome.

7. Missing follow up.

8. All females enrolled in this study were investigated for the serology of systemic lupus erythromatosis (SLE) (Anti DNA antibodies, Antinuclear factor, Ant-histon antibodies and rheumatoid factor), SLE more common in female (5:1 ratio prior to puberty, a 9:1 ratio during reproductive years) [1].

The other 113 patients were first included in this study and then were all excluded because of missing follow up (where 86 patients were excluded from this study because of missing), steroid resistant nephrotic syndrome that mandate the use of immunosuppressant therapy (24 patients were needed immune-suppressant therapy), death (two patients died both were males the 1st because of pulmonary embolism and respiratory failure and the 2nd because of peritonitis and septicemia) and one female patient was excluded for diagnosing SLE (Systemic Lupus Erythromatosis).

A case control study was done for those one hundred four patients, their ages were between 3 and 15 years. Each patient was monitored for duration of 6 months (26 weeks). Patient's follow up visits were scheduled every 2 weeks for the first 8 weeks and then every 4 weeks until the end of the study.

Data collected in this study included: age, sex, time of diagnosis, blood pressure was measured by accurate mercurial sphygmomanometer and using a cuff of which the bladder length covered between 80% and 100% of the upper arm circumference, patients rested in sitting position (or supine, depending on the age of the subject) for 5 minutes before 3 BP measurements were obtained half hour apart, the mean of these readings was used as the subject's blood pressure and the pediatric blood pressure normogram for age and sex was used to diagnose hypertension as systolic and / or diastolic BP > 95th percentile. Laboratory tastes were done by collecting venous blood samples which include: measurement of blood urea nitrogen, serum creatinine and creatinine clearance, serum potassium , hemoglobin level, liver enzymes (serum glutamate pyruvate transaminase, serum glutamic-oxaloacetic transaminase and serum alkaline phosphatase), C3 and C4 complement level, screening for hepatitis Bs antigen and anti-hepatitis C antibody , renal function tests, general urine examination and albumin in urine, abdominal ultrasound and percutaneous renal biopsy .

Study Design:

The study was conducted on 104 patients referred to the nephrology department of three pediatric hospitals in Baghdad:

1. The Central Pediatric Hospital.
2. Al-ElWYIA Pediatric Hospital
3. Ibn Al-Baladi Hospital.

All the nephrotic patients were treated with prednisolone tablet 60 mg/ m^2 body surface area/day and diuretics to decrease body edema.Nephrotic patients were divided randomly to four equal groups and hypertensive patients were divided to the 1st three groups as a following:

1- Group one: Twenty six nephrotic patients with 13 patients had hypertension (systolic blood pressure >95th percentile) at the time of disease diagnosis. All the patients were treated by propranolol 2mg/kg body weight divided to 2 equal doses.
2- Group two: Twenty six nephrotic patients with 13 patients had hypertension at the time of disease diagnosis. All the patients were treated by Angiotensin converting enzyme inhibitor (ACEI) captopril in the dose of 2mg/kg body weight divided to 2 equal doses .
3- Group three: Twenty six nephrotic patients with 12 patients had hypertension at the time of disease diagnosis. All the patients were treated by Angiotensin receptor blocker (ARB) valsartan (DIOVAN®)in the dose of 20 mg, 40 mg, and 80 mg for (< 18 kg), (18-35 kg) and (> or equal to 35 kg) of the patient's body weight respectively, given once at night before sleep.
4- Group four: Twenty six nephrotic patients with normal blood pressure. They were selected as a control in this study.

Note: Some of the hypertensive patients were needed larger dose of antihypertensive medication to control the hypertension.

STATISTICAL METHODS:

Data were entered into Statistical Package for Social Science (SPSS) program for Windows version 20 to generate the general characteristics of the study. Quantitative variables were summarized by finding mean ± SD. Statistical analysis Differences between patients and control were tested with the independent t-test, x2 test and C-test to identify the potential risk factors. A two-tailed P-value of less than 0.05 was considered to be statistically significant.

RESULTS:

Figure one shows that 36 (34.6%) patients were female and 68 (65.4%) were male (p-value=0.02).

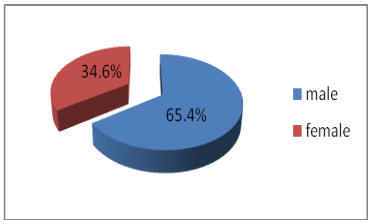

Figure 1: Nephrotic patients regarding sex.

Figure two shows that 75 (72.2%) nephrotic patients in this study their ages were between three to eight years old and 29 (27.8%) patients were older than 8 years (p-value= 0.01).

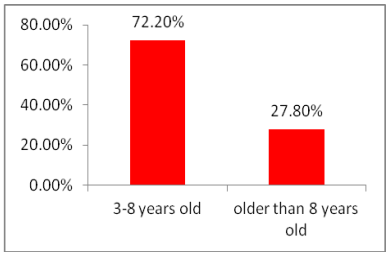

Figure2: Ages of nephrotic patients.

Table one shows that 38 patients (36.5%) were hypertensive at time of disease diagnosis, 60.5% of them theirs ages were 3-8 years but there is no significant relation between patients age and risk of hypertension(P- value=0.08).

Table 1: Blood pressure percentile in newly diagnosed nephrotic patients.

Age	Blood pressure				Total	p-value
	<95th percentile No.	%	≥95th percentile No.	%	No.	
3-8 years	52	78.8	23	60.5	75	0.08
>8 years	14	21.2	15	39.5	29	
Total	66	63.5	38	36.5	104	

Table two shows that mean± SD daily decrease of albumin in urine was more in group three (160.3±34 mg of albumin in urine /day) while in group two, it was 111.1±52mg albumin in urine/day; in group one, it was 76.9± 28 mg albumin in urine/day and in group four (the control patients) , it was 52.4±21mg albumin in urine/day.

Table two shows that valsartan was significantly decrease the albumin in urine(P value=0.003) while captopril was less significant (p value=0.01) while propranolol had no effect on albumin in urine (P- value= 0.08).

Table 2: Mean decrease of albumin in urine/day in nephrotic patients.

Patients group	Mean decrease of albumin in urine mg/day ±SD	P- value
Gruop1	76.9± 28 mg	0.08
Group2	111.1±52mg	0.01
Group3	160.3±34 mg	0.003
Group4	52.4±21mg	

Mean± SD ($\pm t_{0.05/2}\ \sigma_{n-1}/\sqrt{n}$)

Table three shows that albumin in urine back to normal at 26th day in group one , at 18th day in group two, at 12th day in group three and at 27th day in group four. P- values were 0.07, 0.01, 0.004 respectively which were significant in group 2 but more significant in group 3.

Table 3: days by which albumin in urine decrease to normal.

Patients group	days by which albumin in urine decrease to normal	P value
Gruop1	26th day	0.07
Group2	18th day	0.01
Group3	12th day	0.004
Group4	27th day	

Significant hyperkalemia i.e. more than 5.5 meq/dl didn't occur in any patient during therapy time of the four groups as shown in figure 3.

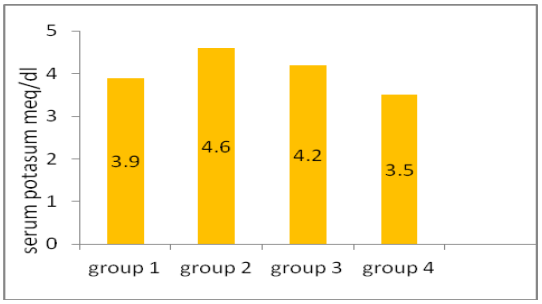

Figure 3: Serum potassium in nephrotic patients.

The serum creatinine increased during therapy time by 10% of the basal measurement of serum creatinine in group1, 18% in group 2, 10% in group 3 and 9% in group 4 as shown in figure 4. Serum creatinine was not significantly affected by drug therapy(P-values were 0.08, 0.1and 0.09 respectively).

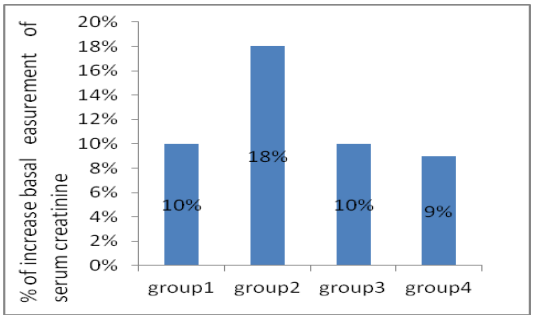

Figure 4:The percentage of increase in basal measurement of serum creatinine.

Mean hemoglobin level after treatment started was 10±2.3gm/dl in group 1, 9.4±1.4gm/dl in group 2, 10.3±1.3gm/dl in group 3 and 11.2±1.4gm/dl in group 4 as shown in table 4. Mean hemoglobin level at time of disease diagnosis were near normal as shown in table 4 . Mean hemoglobin level was not affected by drug therapy (P-value were 0.1, 0.08 and 0.09 respectively).

Table 4: Mean serum hemoglobin in nephrotic patients.

Nephrotic patients	Mean serum hemoglobin at time of disease diagnosis ±SD in gm/dl	Mean serum hemoglobin during therapy ±SD in gm/dl
Group 1	11.1±0.8gm	10±2.3gm
Group 2	10.9±1.3gm	9.4±1.4gm
Group 3	11.2±1.8gm	10.3±1.3
Group 4	11.8±1.1gm	11.2±1.4gm
Mean± SD ($\pm t_{0.05/2}\ \sigma_{n-1}/\sqrt{n}$)		

Treatment in the form of iron, folic acid, and vitamin B12 supplementation were needed in four patients in group2, two patients in group 1 and 3 but none in group 4.

Liver enzymes levels didn't increase above the upper normal levels in any patients of the 4 groups as shown in table 5. P-values were 0.09,0.6 and 0.7 respectively which were not significant.

Table 5: Mean of liver function tests in nephrotic patients.

Nephrotic patients	Mean of liver function tests		
	SGOT U/l	SGPT U/l	serum alkaline phosphatase U/l
Group 1	34±8	31±4	244±35
Group 2	41±5	25±5	215±56
Group 3	31±9	29±8	312±42
Group 4	33±7	23±6	234± 76
Mean± SD ($\pm t_{0.05/2}\ \sigma_{n-1}/\sqrt{n}$)			

DISCUSSION:

Figure one and two shows males were affected more than females (P-value=0.02) and idiopathic nephrotic syndrome is more prevalent in patients their ages were 3-8 years (p-value=0.01). In Taiwan and Iran, idiopathic nephrotic syndrome also was more frequent in boys and those whose their ages 2-6 years [10,11].

Hypertension was diagnosed in 36.5% of the patients newly diagnosed with idiopathic nephrotic syndrome (as shown in table one) with no relation with patients age (p-value=0.08). In Nigeria, 41.4% of the newly diagnosed patients with nephrotic syndrome whose their ages younger than 15 years old were hypertensive with equal effect in those younger and older than 7 years [12].

A number of well-executed, randomized, controlled trials have shown that inhibition of the renin–angiotensin–aldosterone system by either ACE inhibitors or ARBs has a specific renal protective effect in patients with different renal disorders e.g. diabetic nephropathy[13], and in IgA nephropathy [14]. So this study was designed to compare the antiproteinuric effect of Valsartan with other antihypertensive drugs, all achieving comparable blood pressure control.

Tables two and three shows statistically significant rapid decrease in the proteinuria to normal with valsartan than captopril and propranolol. Our result was comparable to the result of a study of Hanneke Buter, et al which showed that the antiproteinuric response was present to the full extent within 7 days of treatment with Losartan while in our study was within 12 days, this because the latter study was conducted on adult diabetic patients and the parameter was microalbuminuria rather than nephrotic range albuminuria (in our study) and using losartan treatment and in our study we use valsartan [15]. The superior effect of Valsartan over Captopril has been suggested that "AngII (angiotensin II) escape" prevents complete RAAS(Renin-Angiotensin-Aldosterone System) inhibition during therapy with an ACEI, due to alternative non-ACE pathways. AngII synthesis via non-ACE pathways (Chymase, chymostatin-sensitive AngII-generating enzyme [CAGE]) has been shown to be more significant, particularly when organ damage has occurred. Another limitation of ACEIs might be the minimal effect on local AngII production via classical ACE pathway[5]. Since ARBs have a direct impact on

AT1(type 1 angiotensin II receptors), AngII escape observed during therapy with an ACEI will not occur with an ARBs. Complete and selective blockade of the AT1 receptor may inhibit all harmful effects of Ang II, systemic or local. However, blocking the receptor leads to a neurohumoral feedback–mediated increase in the level of Ang II molecules, which in turn bind to other AT receptors (angiotensin II receptors) (eg, AT2, AT3, and AT4) that are not blocked by ARBs. AT3 and AT4 have unknown effects and although AT2 has been reported to have an opposite action to that of AT1, potentially unfavorable effects of AT1 such as apoptosis, proinflammatory signal transduction, or chemokine induction which all increase the renal injury and proteinuria besides that the additive "protective" effect of liberating bradykinin by AT2. ARBs may moderate local vascular pressure, cellular hypertrophy and proliferation, and collagen deposition in the kidneys more completely than ACEIs resulting in greater target protection[15,16].

Regarding the Valsartan safety, as our study showed no patient developed dangerous increase in serum potassium, renal function or liver function parameters (as shown in figure3, 4 and table 5). A study done in China, 122 patients with non diabetic renal diseases were treated with valsartan, captopril and placebo. Serum Creatinine significantly increased from 1.9 +/- 0.5 to 2.3 +/- 0.8 mg/dl in placebo and 1.8 +/- 0.7 to 2.8 +/- 0.5 mg/dl ($p < 0.008$) in captopril periods , but the changes were insignificant in the valsartan period (2.1 +/- 0.6 to 2.2 +/- 0.9 mg/dl). During the valsartan period, urinary protein excretion was less than that during the captopril and placebo periods (0.75 +/- 0.73 vs. 1.24 +/- 0.92 and 1.43 +/- 0.83 g/g Cr, $p < 0.001$ and 0.002 respectively). Serum K was significantly higher in the valsartan and captopril periods than in the placebo period (4.6 +/- 0.5 and 4.8 +/- 0.6 respectively vs. 4.4 +/- 0.5 mEq/l in placebo, $p < 0.05$); however, no patients discontinued taking valsartan as a result of hyperkalemia [17] . In mild to moderate liver impairment, no adjustment necessary in valsartan dose [18].

Regarding Hyperkalemia one possible explanation for the greater tendency to develop hyperkalemia with the Angiotensin converting enzyme (ACE) inhibitor is the greater suppression of plasma aldosterone levels with ACE inhibition compared to angiotensin receptor blockade and so far as hyperkalemia can be life threatening, the angiotensin receptor blockers (ARBs) may impart a greater safety advantage in patients in need of rennin-angiotensin-aldosterone system (RAAS) inhibition [19]. Hyperkalemia secondary to beta-adrenergic receptor blockade occurs in 1-5% of patients and is likely to develop with non-cardioselective beta-blockers. Hyperkalemia can be unpredictable and life threatening complication of propranolol or non-selective adrenergic beta blocker treatment, and requires timely identification and implementation of therapeutic measures [20].

Mean hemoglobin level was not affected significantly by drugs therapy as seen in table 4. Yayoi Nishida, et al study shows greater reductions of hemoglobin and hematocrit values and greater increase of serum potassium level in patients who had received ARBs and ACE inhibitor monotherapy compared with calcium channel blockers although the mean values of these parameters remained within normal limits during the baseline and exposure periods, no patients need to stop treatment [21]. A study done by Adnan Ajmal, et al on patients treated with ACE inhibitor and ARBs, they found that use of ACE inhibitors was associated with a lower hemoglobin at follow up, while ARBs was not. The difference was small but statistically significant[22]. A study done on 2478 patients on propranolol therapy, only eight of them were develop iron deficiency anemia[23].

CONCLUSION: Valsartan (angiotensin receptor blockers) has rapid and consistent antiproteinuric effect even beyond its antihypertensive effect in children with minimal changes nephrotic syndrom in comparison with captopril (angiotensin converting enzyme inhibitors) and propranolol (B-blocker).

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