doi.org/10.36721/PJPS.2021.34.6.SP.2441-2445.1

Clinical nephrotoxicity induced by cyclosporin A combined with hormone therapy for nephrotic syndrome

Xiaoli Liu[1], Guiying Li[2*], Xin Liu[1], Yansong Huang[3], Zhijie Xun[3], Qian Song[3], Ruixia Wang[4] and Congmin Wang[1]

[1]Affiliated Hospital of Hebei Engineering University, Handan, Hebei, China
[2]Medical College, Hebei University of Engineering, Handan, Hebei, China
[3]Handan First Hospital, Handan, Hebei, China
[4]Handan Second Hospital, Handan, Hebei, China

Abstract: This study aims to explore the nephrotoxicity due to use of combination of cyclosporine A and hormone in the treatment of nephrotic syndrome. From January 2018 to November 2019, 100 patients with primary nephrotic syndrome were divided into experimental and control groups, with 50 patients per group. The experimental group took oral cyclosporine A and prednisone tablets, while the control group received oral cyclosporine A combined with shock therapy. The contents of white blood cells, triglycerides, urine protein and cholesterol in the experimental group were lower than those in the control group, while their albumin content was significantly higher than the control values. Blood concentrations of cyclosporine A were significantly lower in non-nephrotoxic patients than in nephrotoxic patients. The high blood cyclosporine A level in patients (>200ng/mL) may be a factor for inducement of nephrotoxicity. Basal serum creatinine levels in nephrotoxic patients were significantly higher than those in non-nephrotoxic patients. Therefore, high basal creatinine level may be a contributing factor to nephrotoxicity. The combination of cyclosporine A and hormone is effective in the treatment of nephrotic syndrome. Blood cyclosporine A levels greater than 200ng/ml or elevated basal serum creatinine may be the cause of nephrotoxicity.

Keywords: Cyclosporine A, hormones, combination, nephrotic syndrome, treatment, nephrotoxicity, clinical observation

INTRODUCTION

Cyclosporin A is most commonly used in the treatment of renal disease. The bioactive principle in cyclosporin A is a circular polypeptide composed of 11 amino acids (Hamasaki *et al.*, 2017; Sugimoto *et al.*, 2017; Yu *et al.*, 2017). This drug inhibits the synthesis of calcineurin, reduces the transcriptions of various cytokines in patients, suppresses humoral/cellular immunity of patients and exerts high inhibitory effect on the proliferation of lymphocytes (Querfeld and Weber 2018; Kondo *et al.*, 2020). In recent years, studies have found that cyclosporin A has a significant repair effect on renal podocyte, and it has been widely used in the treatment of nephrotic syndrome. In addition, it is used to treat some intractable kidney diseases caused by pathologies. With deepening of medical research, it has been found that the use of cyclosporin A in the treatment of kidney disease may cause renal vasoconstriction and glomerular artery contraction, leading to kidney damage and renal toxicity (Lebel *et al.,* 2020). In this study 20 out of 100 patients treated with cyclosporine A for comprehensive nephropathy showed nephrotoxicity. From January 2018 to Nov 2019, 100 patients with primary NS diagnosed with renal pathology in our hospital were studied.

*Corresponding author: e-mail: liuyuhe_123@126.com

MATERIALS AND METHODS

General materials

A total of 100 patients with primary nephrotic syndrome diagnosed using renal pathology in our hospital from January 2018 to November 2019 were selected as study subjects. The ages of the patients ranged from 15 to 70 years (mean age = 46.39±12.71 years). There were 63 male patients and 37 female patients. The duration of disease ranged from 6 months to 2 years (mean duration = 1.06±0.24 years). There were 22 cases of primary membranous nephropathy, 21 cases of primary focal segmental sclerosis, 19 cases of severe mesangial proliferative glomerulonephritis, 18 cases of membranous glomerulonephritis and 20 cases of other disease types.

Inclusion criteria

All patients who were diagnosed with nephrotic syndrome were included. The included subjects had not developed widespread infection in three months and had not taken large doses of antibiotics.

Exclusion criteria

Patients with viral hepatitis, drug contra-indications, diabetes, severe respiratory failure and congenital heart disease were excluded.

The study was approved by the Ethics Committee of our hospital and all patients and their families were aware of

the purpose of the study and methods used and they signed informed consent to participate in this study.

Methods

Patients in the experimental group were treated with cyclosporin A combined with prednisone. The initial dose of cyclosporin A was 5 to 6ml/kg/day, twice a day, which was taken orally on an empty stomach. The interval between the two doses was 12 hours. The blood concentration of cyclosporin A was measured regularly, and the dose was adjusted according to patients' recovery. Prednisone tablets were given orally at a dose of 30mg/day for 8 weeks and the dose was gradually reduced. Subjects in the control group received cyclosporin A orally, in combination with shock therapy. The route of administration of cyclosporin A was the same as that of the experimental group. For shock therapy, cyclophosphamide was adopted at a dose of 0.6g for two days every month for 6 months. The effects of treatments on the patients were recorded. Patients whose serum creatinine levels increased by more than 30%, when compared to the basic value were recorded as showing nephrotoxicity, while those whose serum creatinine level increased by less than 30% were recorded as the non-nephrotoxic group (Chen *et al.*, 2020b; Chen *et al.*, 2020a; Hejazian *et al.*, 2020). Plasma concentrations of cyclosporin A, total cholesterol, and basal creatinine levels were compared between the two groups.

Observation indices

If the patient's urine protein within 24 hours was less than 0.15, with stable renal function, and the plasma albumin was greater than 35g /L, such a patient was in complete remission. If the quantitative urine protein of a patient within 24 hours was reduced to 50% of the basal level, with content less than 3.5g and the renal function was stable, the patient was in partial remission. Patients with urinary protein greater than 3.5g within 24 hours, or less than 50% reduction compared to the basal level, were considered as patients for whom treatment failed. Patients with elevated serum creatinine levels greater than 30% of baseline value were classified as showing nephrotoxicity, while those with elevated serum creatinine levels less than 30% of basal value were placed in non-nephrotoxicity group.

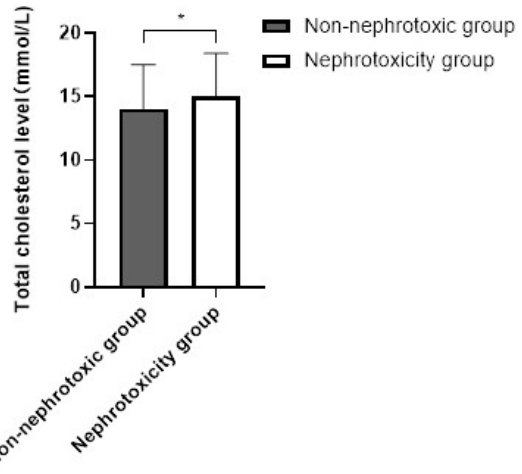
STATISTICAL ANALYSIS

In this study, all relevant data were processed with SPSS 21.0 software. Measurement data are expressed as mean ± standard deviation (SD), and they were statistically analyzed using *t*-test. Count data are presented as n (%), and were analyzed with Chi square test. Values of $p<0.05$ were considered as indicative of statistically significant differences.

RESULTS

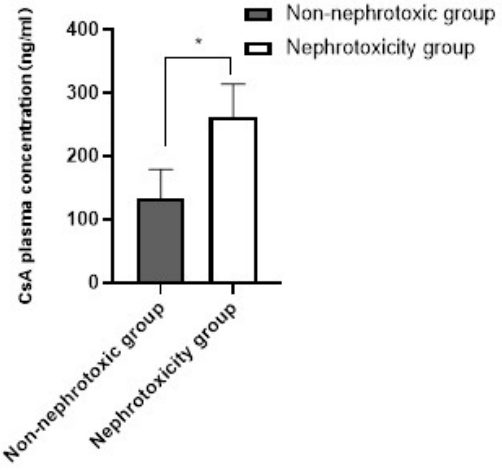
Comparison of white blood cell, albumin, and triglyceride levels

Before treatment, there were no significant differences in the contents of white blood cells, albumin and triglycerides between the two groups. However, after treatment, the levels of white blood cells, triglycerides and albumin in the experimental group were significantly lower than those in the control group, while the content of albumin was higher in the experimental group ($p<0.01$). These results are presented in table 1.



* represents difference in total cholesterol level between patients with nephrotoxicity and those without nephrotoxicity. The difference was not statistically significant (t =1.1376; p=0.258).

Fig. 1: Comparison of total cholesterol levels between nephrotoxic and non-nephrotoxic patients. The abscissa represents the groups; the ordinate is the total cholesterol level. The total cholesterol level of patients with nephrotoxicity was 15.01±3.4mmol/L, while the total cholesterol level of non-nephrotoxic patients was 14.02±3.5mmol/L.



The abscissa represents the groups, while the ordinate represents the blood concentration of cyclosporin A. Plasma concentration

of cyclosporin A in patients with nephrotoxicity was 262.15±52 ng/ml, while plasma concentration of cyclosporin A in non - renal toxicity patients was 133.02±46 ng/ml. * Difference in plasma concentrations of cyclosporin A between patients with nephrotoxicity and those without (t=19.9001, p<0.001).

Fig. 2: Comparison of plasma concentrations of cyclosporin A between patients with nephrotoxicity and those without.

Comparison of urinary protein, cholesterol and serum creatinine levels

No significant differences were found in urinary protein and cholesterol content between the two groups, before treatment. However, after treatment, the urinary protein and cholesterol contents of the experimental group were significantly lower than the corresponding values in the control group (p<0.01; table 2).

Effect of treatment and incidence of nephrotoxicity

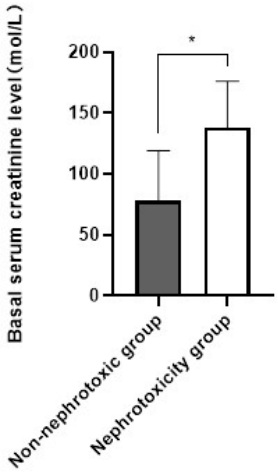
The effect of treatment and occurrence of nephrotoxicity in patients with different types of nephropathy are shown in table 3.

Comparison of total cholesterol levels

As shown in fig. 1, there was no statistically significant difference in total cholesterol levels between patients with nephrotoxicity and those without nephrotoxicity (p>0.05).

Comparison of plasma concentrations of cyclosporin A

fig. 2 shows that the blood concentration of cyclosporin A in patients with nephrotoxicity (more than 200ng/mL) was significantly lower than in those without nephrotoxicity (p<0.01). Therefore, blood concentration of cyclosporin A higher than 200ng/mL may be a contributory factor for nephrotoxicity in patients.



The abscissa represents the groups, while the ordinate represents the patient's baseline creatinine level. The serum creatinine level of patients with nephrotoxicity was 138.03±38 mol/L. The serum creatinine level of non-nephrotoxic patients was 78.06±41 mol/L. * Represents the difference in serum creatinine between patients with nephrotoxicity and those without (t = 5.9323; p < 0.001).

Fig. 3: Comparison of baseline creatinine levels between patients with nephrotoxicity and those without.

Comparison of baseline creatinine levels

The basic creatinine level of patients with nephrotoxicity was significantly higher than that of patients without nephrotoxicity (p<0.01; fig. 3). Therefore, high creatinine level may be a factor leading to nephrotoxicity.

DISCUSSION

Nephrotoxicity is a renal toxicity reaction caused by drugs. The kidney is an important excretory organ of human body, and it is easily damaged by exposure to drugs (Chan *et al.*, 2020; Mollazadeh *et al.*, 2018; Meena *et al.*, 2020). The clinical manifestations of nephrotoxicity vary greatly. The earliest symptom is cylinderuria and proteinuria, leading to renal insufficiency, and in severe cases, uremia and acute renal failure (Rathore *et al.*, 2020).

Primary nephrotic syndrome (PSNS) is a common kidney disease. It is a disorder of the immune system that causes inflammation, leading to varying degrees of glomerular reaction. In the treatment of such diseases, hormone use is the main strategy (Downie *et al.*, 2017). However, for comprehensive nephropathy which is difficult to treat clinically, hormone therapy alone does not produce appreciable effects. In this case, cyclosporine A combined with hormone therapy is required for treatment. However, cyclosporin A has A dual effects in the treatment of comprehensive nephropathy: not only does it reduce inflammation in patients, it also inhibits the proliferation of glomerular mesangial cells to a certain extent, resulting in a series of complications (Rahman *et al.*, 2019). Many clinical studies have shown that although the combination of cyclosporin A and hormone therapy is effective to certain degree, renal toxicity may occur. In the present study, 20 out of 100 patients with comprehensive nephropathy were nephrotoxic (Pınarbaşı *et al.*, 2019). There were no significant differences in the contents of white blood cells, albumin, triglycerides, urinary protein and cholesterol between the two groups, before treatment. After treatment, the content of white blood cells, triglycerides, urine protein and cholesterol in the experimental group were lower than those in the control group and the content of albumin was markedly higher than that in the control group. No statistically significant difference was found in total cholesterol between the nephrotoxic and non-nephrotoxic patients. Blood concentrations of cyclosporin A in patients with nephrotoxicity and those without nephrotoxicity were significantly lower than that in patients with renal toxicity. Thus, blood concentration of cyclosporin A higher than 200ng/mL may lead to the occurrence of nephrotoxicity in patients. The basic creatinine level of patients with

Table 1: Comparison of levels of white blood cell, albumin, and triglycerides between the two groups [n, ($\bar{x}$±s)]

Group	n	WBC (L)		Albumin (g/L)		Triglycerides (mol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental	50	7.21±1.11	4.21±1.12	22.43±4.26	36.29±4.07	3.50±0.6	1.59±1.01
Control	50	7.26±1.11	5.69±1.21	22.50±4.26	31.1±1.11	3.55±0.7	2.21±1.02
t		0.225	6.347	0.082	8.699	0.383	3.054
P		0.822	<0.001	0.934	<0.001	0.702	0.003

Table 2: Comparison of urinary protein, cholesterol and serum creatinine levels between the two groups [n, ($\bar{x}$±s)]

Group	n	Urinary protein (g)		Cholesterol (mol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Experimental	50	5.2±0.91	1.7±0.82	12.4±2.1	6.6±2.11
Control	50	5.2±0.81	3.4±0.82	12.1±2.2	9.5±2.13
t		0	10.365	0.6974	6.8395
P		1	<0.001	0.4872	<0.001

Table 3: Therapeutic effect and incidence of nephrotoxicity in patients with different nephropathy types (n, %)

Pathological type		Efficacy			Nephrotoxicity
		Complete remission	Partial remission	Ineffective	
FSGS	21	47.6% (10/21)	23.8% (5/21)	28.6% (6/21)	14.3% (3/21)
MN	22	40.9% (9/22)	22.7% (5/22)	36.4% (8/22)	27.3% (6/22)
MsPGN	19	47.4% (9/19)	42.1% (8/19)	10.5% (2/19)	21.1% (4/19)
MPGN	18	16.7% (7/18)	16.7% (9/18)	16.7% (2/18)	16.7% (3/18)
Others	20	45% (9/20)	30% (6/20)	25% (5/20)	20% (4/20)
Total	100	44% (44/100)	33% (33/100)	23% (23/100)	20% (20/100)

(MN=membranous nephropathy; FSGS=focal segmental glomerular sclerosis, MsPGN=mesangial proliferative glomerulonephritis; MPGN=mesangial proliferative glomerular nephritis). During the treatment course, 20 patients developed nephrotoxicity.

nephrotoxicity was significantly higher than that of patients without nephrotoxicity. Therefore, high serum creatinine levels may be a predisposing factor for nephrotoxicity. The results obtained in this study are similar to those reported earlier in a study on a very rare unexpected fatal complication of nephrotic syndrome (Etta *et al.*, 2019). In that study, it was suggested that high creatinine levels contribute to nephrotoxicity in patients.

CONCLUSION

The use of cyclosporin A in combination with hormone therapy for nephrotic syndrome produces significant therapeutic efficacy. Blood concentration of cyclosporin A greater than 200ng/ml, or the high level of blood creatinine are factors that contribute to nephrotoxicity in patients.

REFERENCES

Chan TYK, Chan APL and Tang HL (2020). Nephrotic syndrome caused by exposures to skin-lightening cosmetic products containing inorganic mercury. *Clin. Toxicol. (Phila),* **58**(1): 9-15.

Chen HX, Cheng Q, Li F, He QN, Cao Y, Yi ZW and Wu XC (2020a). Efficacy and safety of tacrolimus and low-dose prednisone in Chinese children with steroid-resistant nephrotic syndrome. *World J. Pediatr.,* **16**(2): 159-167.

Chen X, Wang DD, Xu H and Li ZP (2020b). Optimization of initial dosing scheme of tacrolimus in pediatric refractory nephrotic syndrome patients based on CYP3A5 genotype and coadministration with wuzhi-capsule. *Xenobiotica,* **50**(5): 606-613.

Downie ML, Gallibois C, Parekh RS and Noone DG (2017). Nephrotic syndrome in infants and children: pathophysiology and management. *Paediatr Int. Child Health,* **37**(4): 248-258.

Etta PK, Reddy S, Rao MV and Thatipamula M (2019). A very rare unexpected fatal complication of nephrotic syndrome. *Indian J. Nephrol.,* **29**(6): 435-437.

Hamasaki Y, Komaki F, Ishikura K, Hamada R, Sakai T, Hataya H, Ogata K, Ando T and Honda M (2017). Nephrotoxicity in children with frequently relapsing nephrotic syndrome receiving long-term cyclosporine treatment. *Pediatr Nephrol.,* **32**(8): 1383-1390.

Hejazian SM, Zununi Vahed S, Moghaddas Sani H, Nariman-Saleh-Fam Z, Bastami M, Hosseiniyan

Khatibi SM, Ardalan M and Samadi N (2020). Steroid-resistant nephrotic syndrome: Pharmacogenetics and epigenetic points and views. *Expert Rev Clin Pharmacol.,* **13**(2): 147-156.

Kondo H, Watanabe R, Okazaki S, Kuriyama K, Ochi T, Yamada G, Sugiura A, Chiba H, Tsukada A, Taniuchi S, Igarashi T, Kudo M, Harigae H and Fujii H (2020). JAK2 mutation-positive polycythaemia vera associated with IgA vasculitis and nephrotic syndrome: A case report. *Mod. Rheumatol Case Rep.,* **4**(2): 289-295.

Lebel A, Kropach N, Ashkenazi-Hoffnung L, Huber-Yaron A and Davidovits M (2020). Infections in children with nephrotic syndrome: Twenty years of experience. *Clin Pediatr (Phila),* **59**(7): 692-698.

Meena J, Sinha A, Hari P and Bagga A (2020). Therapy with the combination of tolvaptan and furosemide for refractory edema in nephrotic syndrome. *Indian J. Nephrol.,* **30**(1): 53-55.

Mollazadeh S, Sahebkar A, Hadizadeh F, Behravan J and Arabzadeh S (2018). Structural and functional aspects of P-glycoprotein and its inhibitors. *Life Sci,* **214**118-123.

Pınarbaşı AS, Dursun I, Daldaban B, Günay N, Çiçek S, Şahin N, Yel S, Poyrazoglu MH, Akgün H and Düşünsel R (2019). Epidermolysis bullosa complicated with nephrotic syndrome due to AA amyloidosis: A case report and brief review of literature. *Saudi J Kidney Dis Transpl,* **30**(6): 1450-1456.

Querfeld U and Weber LT (2018). Mycophenolate mofetil for sustained remission in nephrotic syndrome. *Pediatr Nephrol,* **33**(12): 2253-2265.

Rahman MA, Rahman MH, Karim MR and Huque SS (2019). Multiple loculated peritoneal abscesses in a child with nephrotic syndrome: A rare presentation. *Saudi J Kidney Dis Transpl,* **30**(6): 1475-1478.

Rathore V, Bhattacharya D, Pandey J, Bhatia A, Dawman L and Tiewsoh K (2020). Chylothorax in a child with nephrotic syndrome. *Indian J. Nephrol,* **30**(1): 32-34.

Sugimoto K, Miyazawa T, Enya T, Miyazaki K, Okada M and Takemura T (2017). Cyclosporine A induced histological changes of Cathepsin L and CD2AP expression in renal glomeruli and tubules. *Clin. Exp. Nephrol.,* **21**(1): 83-91.

Yu X, Ruan L, Qu Z, Cui Z, Zhang Y, Wang X, Meng L, Liu X, Wang F, Zhang Y, Liu G and Yang L (2017). Low-dose cyclosporine in treatment of membranous nephropathy with nephrotic syndrome: Effectiveness and renal safety. *Ren Fail.,* **39**(1): 688-697.