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Brief Report

The Effect of High-Flux Dialysis Combined with Hemoperfusion to Eliminate Indoxyl Sulfate in Dialysis Patients

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Abstract

Indoxyl sulfate is a protein binding urotoxin, which is discharged by the kidney through secreted in proximal tubule and accumulates in patients with renal failure, It can cause the endothelial dysfunction and cardiovascular disease. Due to has a high affinity for albumin, cannot effectively remove by hemodialysis and hemodiafiltration. Therefore, protein-bound urinary toxins have become a focus of renal replacement treatment.We used high flux dialysis combined with hemoperfusion for treatment, and found that the clearance of indoxyl sulfate was higher than high flux dialysis and hemodiafiltration, and 4 hours was better than 2 hours.

Keywords: Hemodiafiltration; Hemodialysis; Hemoperfusion; Indoxyl sulfate

Introduction

Indoxyl sulfate which a protein-bound uremic toxins are excreted by the kidneys via proximal tubular secreti[1], Consequently, they accumulate in the blood of patients with impaired renal function [1,2] and affect endothelial barrier function, endothelial cell proliferation and wound repair also [3], the levels correlated with aortic calcification, and in addition also with vascular stiffness [4,5]. increasingly evidences suggests that protein-bound uremic toxins play an important role in complications, especially in cardiovascular disease [6,7]. Notably, protein-bound uremic toxins have emerged as focus targets of therapeutic removal [6]. Moreover, they cannot be efficiently removed by conventional haemodialysis and hemodiafiltration [8], due to their high binding affinity for albumin [1,2,9], which are poorly eliminated by the commonly used dialysis techniques; Studies had shown that protein binding uremic toxins can absorb in intestine by oral adsorbents and hemodialysis combine adsorbents in order to clear it out from blood.Therefore, we are eager to know the variation of the clearance rates of water-soluble and protein bound uremic toxins by different blood purification methods, including High Flux Dialysis (HD), Hemodiafiltration (HDF), High Flux Dialysis Combine With Hemoperfusion (HD+HP).

Materials and Methods

Five volunteers (4 male and 1female) from Tangshan Likang Hospital received hemodialysis three times a week more than three years, body weight 80.9 ± 2.3Kg.All patients were sampled 10ml of blood, at 0 and 2 and 4 hrs during hemodialysis or hemodiafiltration or hemodialysis combined with perfusion, then immediately centrifuge at 3000rpm for 15min, and freeze the serum at -70℃. Until detected for BUN, creatinine, phosphorus, β 2-Microglobulin and indoxyl sulfate; All serum sample were assayed by Mindray 85-820M full-automatic biochemical analyzer (Mindray Medical International Co., Ltd, Shenzhen, China). And the Indoxyl sulfate was measured by HPLC using an Agilent 1100 Series system (Agilent Technologies Co. Ltd., Palo Alto, CA, USA). The results are expressed in Mean ± SD, and this study has been approved by the Medical Ethics Committee of Tangshan Likang Hospital (No. 2022112301), all patient's age are more than 18 years old and informed consent. The patient's treatment schedule

is High flux Dialysis (HD) 290ml/min, HD+HP 240ml/min, Hemodiafiltration (post-dilution) 290ml/min, HD+HP 290ml/min. (The prescription was shown as Table 1).

Purification method	Dialyzer	perfusion device	Blood flow (ml/min)	Dialysate flow (ml/min)	exchange volume (L)	durations (hrs)
High flux Dialysis (HD)	OCI-HF200	--	290	500	--	4
Hemodiafiltration (post-dilution)	OCI-HF200	--	290	500	≧15L	4
HD+HP 240ml/min	OCI-HF200	OC-160	240	500	--	4
HD+HP 290ml/min	OCI-HF200	OC-160	290	500	--	4

Table 1: The blood purification prescription for volunteers:Dialysate/exchange solution compound: Na 140meq/L, Ca 1.5mmol/L, Dextrose 5.5mmol/L(100mg/dl), temperature 36°C, dialysate flow rate 500ml/min, treatment for 4 hours. OCI-160 used as perfusion device which containing 160 ml resin (OCI Medical Devices Co., Ltd, Chengdu, China) and all patients were used OCI-HF200 dialyzer (OCI Medical Devices Co., Ltd, Chengdu, China).

Result

All volunteers were followed the doctor's instructions to control a weight gain of 3-4 kilograms (less than 5% BW) during the dialysis interval, their pre dialysis blood pressure was 130-150/80-90mmHg; and after dialysis 120~140/80mmHg; The clearance of water-soluble uremic toxins (BUN, Creatinine, Phosphorus β2-microglobulin) is HDF>HD and HD is equivalent to HD+HP; the clearance rate of indoxyl sulfate is HD+HP>HDF>HD. The clearance rate at 4 hours in all groups is greater than that at 2 hours. The clearance rate of uremic toxins by different blood purification methods are detailed in Table 2.

purification method (n=5)	Sampling		systolic pressure mmHg	Diatolic pressure mmHg	BUN mmol/l	BUN reduction rate %	Creatinine umol/l	Cr reduction rate %	Phosphate mmol/l	P reduction rate %	β 2-microglobulin mg/l	β 2-m reduction rate %	indoxyl sulfate (ng/ml)	IS reduction rate %
HD 290ml/min	0hrs	Mean	154	93	23.3	… …	895.1	… …	1.23	… …	27.4	… …	33418.4	… …
		±SD	7	7	4.4		311.0		0.24		3.5		11457.1	
	2hrs	Mean	137	87	11.8	49%	460.6	49%	0.61	50%	15.6	43%	29834.4	10.72%
		±SD	23	11	3.0		174.3		0.15		2.3		10639.9	
	4hrs	Mean	137	81	7.4	68%	328.9	63%	0.60	51%	12.2	55%	27673.9	17.19%
		±SD	25	8	2.3		126.7		0.14		2.7		9944.4	
HDF 290ml/min	0hrs	Mean	144	91	21.6	… …	942.5	… …	1.23	… …	26.9	… …	37602.3	… …
		±SD	16	12	3.7		279.8		0.20		4.2		8284.8	
	2hrs	Mean	136	83	10.5	51%	462.0	51%	0.58	53%	11.9	56%	31576.2	16.03%
		±SD	15	9	2.3		149.0		0.11		2.4		6729.3	
	4hrs	Mean	126	79	6.3	71%	317.0	66%	0.50	59%	8.2	70%	29031.8	22.79%
		±SD	18	14	1.7		112.8		0.10		1.9		6913.5	
HD+HP 240ml/min	0hrs	Mean	131	84	21.9	… …	931.9	… …	1.21	… …	29.1	… …	33751.7	… …
		±SD	8	6	4.3		246.3		0.32		4.0		9068.1	
	2hrs	Mean	127	79	11.5	48%	494.7	47%	0.58	52%	16.1	44%	24660.4	26.94%
		±SD	8	10	3.0		155.0		0.14		2.7		6266.4	
	4hrs	Mean	120	79	7.4	66%	352.6	62%	0.58	52%	12.2	58%	19735.1	41.53%
		±SD	4	7	2.2		120.4		0.16		2.6		5203.4	
HD+HP 290ml/min	0hrs	Mean	133.8	86.8	133.8	… …	1020.1	… …	1.4	… …	30.5	… …	37892.3	… …
		±SD	14.5	15.4	14.5		243.0		0.4		3.4		11575.5	
	2hrs	Mean	136.2	83.8	136.2	48%	528.1	47%	0.7	52%	19.3	44%	28963.2	23.56%
		±SD	18.8	10.4	18.8		154.3		0.1		2.3		8066.4	
	4hrs	Mean	129.0	85.0	129.0	66%	360.3	62%	0.6	52%	15.2	58%	23502.7	37.98%
		±SD	10.8	6.3	10.8		114.4		0.2		3.2		6885.9	

Table 2: The clearance rate of uremic toxins by different blood purification methods.

Discussion

Indoxyl Sulfate (IS) which a protein bound uremic toxin is derived from tryptophan and metabolized by bacteria in the gastrointestinal tract [10-13], More than 90% of IS in the blood binds to albumin. When kidney function is normal, Blood circulation of IS passes through the kidneys then excreted into urine [13-14]. Indoxyl sulfate is also widely recognized as an endoheliotoxin. The serum levels elevate in advanced stage of Chronic Kidney Disease (CKD) and related to the degree of reduction in glomerular filtration

rate. Therefore, accumulate in the serum of patients with CKD, they may have different clinical impacts in terms of cardiovascular disease and other complication [1,15]. Due to they can induce endothelial dysfunction and cardiovascular disease in CKD patients [11,16,17]. And there were plenty of evidences had pointed out indoxyl sulfate is an independent risk of the cardiovascular disease are correlated with cardiovascular mortality in the patients with renal insufficiency or dialysis patients [18,19]. The serum levels of indoxyl sulfate are approximately 54 times and cardiovascular death in dialysis patients is 10-20 times more than in healthy individuals [15].Therefore, how to eliminate protein bound toxins is a new issue in the dialysis community, The current clinical direction is try to reduce the intestinal generation and absorption, and increasing elimination by kidney in order to reduce the serum level and attenuate the progression of cardiovascular disease [20,21]. The principle of well- known oral adsorbents (AST-120, KREMEZIN), protein bound toxins is absorbed by adsorbents and excreted in the feces before into the bloodstream, thereby reducing the accumulation of IS in CKD patients [11]. However, since the oral binders only affect the intestinal duct, it cannot remove that had taken into the circulation. To eliminate the absorbed protein bound uremic toxins remains a thorny issue.Based on the protein bound uremic toxins are hydrophobic can be adsorbed by hydrophobic adsorbers and most hydrophobic uremic toxins are anionic. They have high binding affinity for albumin and cannot be efficiently removed by conventional haemodialysis and hemodiafiltration [8,22], new strategies for remove hydrophobic uremic toxins are needed. Therefore, use cationic adsorbents to remove protein bound hydrophobic uremic toxins is a new choice [8].

Nowadays, Hemoperfusion adsorder mainly relies on adsorptive materials to remove protein binding uremic toxins, and cannot perform liquid balance and small- molecular and water-soluble uremic toxin clearance alone. Therefore, clinical treatment strategies are optimized by combining HP with HD [23]. Tiranathanagul K, et al. had Compared the effects of high-flux dialyzer with 2 hours of hemofusion and high volume post-dilution online hemodiafiltration on uremic toxin clearance, it was found that HD+HP was not superior to HDF [24].Here, the study found the high flux dialysis combined with hemoperfusion (HP cartridge containing 160 ml resin; OCI Medical Devices Co., Ltd, Chengdu, China) that the clearance of Indoxyl sulfate was higher than high flux dialysis and hemodiafiltration (41.53%, 17.19%, 22.79%), and 4 hours was better than 2 hours (45.53%, 26.94%). However, the clearance of small molecular and water soluble uremic toxins is not superior to high flux dialysis and hemodiafiltration. The clearance effect of HD+HP blood flow rate of 290ml/min is not higher than that of 240ml/min. This phenomenon is consistent with the thesis that too fast flow rate actually leads to decrease the adsorption capacity. Due to the small sample size and the Indoxyl sulfate was needed measured by High Performance Liquid Chromatography Mass Spectrometry (HPLC/MS) in the study limited [25,26]. Although HD+HP has a significant clearance effect on Indoxyl sulfate, but increase the cost and complexity of treatment.

Reference

1. Liabeuf S, Drüeke TB, Massy ZA (2011) Protein-bound uremic toxins: new insight from clinical studies. Toxins (Basel) 3: 911-919.
2. Vanholder R, Schepers E, Pletinck A, Nagler EV, Glorieux G (2014) The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: a systematic review. J Am Soc Nephrol 25: 1897-907.
3. Dou L, Bertrand E, Cerini C, et al. (2004) The uremic solutes p-cresol and indoxyl sulfate inhibit endothelial proliferation and wound repair. Kidney International 65: 442-451.
4. Jourde-Chiche N, Dou L, Cerini C, Dignat-George F, Brunet P (2011) Vascular incompetence in dialysis patients--protein-bound uremic toxins and endothelial dysfunction. Semin Dial 24: 327-337.
5. Wu IW, Hsu KH, Hsu HJ, et al. (2012) Serum free p-cresyl sulfate levels predict cardiovascular and all-cause mortality in elderly hemodialysis patients--a prospective cohort study. Nephrol Dial Transplant 27: 1169-1175.
6. Niwa T (2013) Removal of protein-bound uraemic toxins by haemodialysis. Blood Purif 35: 20-25.
7. Rossi M, Campbell KL, Johnson DW, et al. (2014) Protein-bound uremic toxins, inflammation and oxidative stress: a cross-sectional study in stage 3-4 chronic kidney disease. Arch Med Res 45: 309-317.
8. Brettschneider F, Tölle M, von der Giet M, et al. (2013) Removal of protein-bound, hydrophobic uremic toxins by a combined fractionated plasma separation and adsorption technique. Artif Organs 37: 409-416.
9. Viaene L, Annaert P, de Loor H, Poesen R, Evenepoel P, et,al (2013) Albumin is the main plasma binding protein for indoxyl sulfate and p-cresyl sulfate. Biopharm Drug Dispos 34: 165-175.
10. Guerrero F, Carmona A, Jimenez MJ, et al (2021) Passage Number-Induced Replicative Senescence Modulates the Endothelial Cell Response to Protein-Bound Uremic Toxins. Toxins (Basel) 13: 738.
11. Asai M, Kumakura S, Kikuchi M. (2019) Review of the efficacy of AST-120 (KREMEZIN®) on renal function in chronic kidney disease patients. Ren Fail 41: 47-56.
12. Agus A, Planchais J, Sokol H (2018) Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. Cell Host Microbe 23: 716-724.
13. Hobby GP, Karaduta O, Dusio GF, Singh M, Zybailov BL et,al (2019) Chronic kidney disease and the gut microbiome. Am J Physiol Renal Physiol 316: F1211-1217.
14. Iwasaki Y, Yamato H, Nii-Kono T et al (2006) Uremic toxin and bone metabolism. J Bone Miner Metab24: 172-175.
15. 1Ito S, Yoshida M (2014) Protein-bound uremic toxins: new culprits of cardiovascular events in chronic kidney disease patients. Toxins (Basel) 6: 665-678.
16. Lin CJ, Pan CF, Liu HL, et al. (2012) The role of protein-bound uremic toxins on peripheral artery disease and vascular access failure in patients on hemodialysis. Atherosclerosis 225: 173-179.

17. Lano G, Burtey S, Sallée M (2020) Indoxyl Sulfate, a Uremic Endotheliotoxin. Toxins 12: 229.

18. Brunet P, Gondouin B, Duval-Sabatier A, et al.(2011) Does uremia cause vascular dysfunction? Kidney Blood Press Res 34: 284-290.

19. Yamamoto S, Sato M, Sato Y, et al. (2018) Adsorption of Protein-Bound Uremic Toxins Through Direct Hemoperfusion With Hexadecyl-Immobilized Cellulose Beads in Patients Undergoing Hemodialysis. Artif Organs 42: 88-93.

20. Poesen R, Viaene L, Verbeke K, et al. (2014) Cardiovascular disease relates to intestinal uptake of p-cresol in patients with chronic kidney disease. BMC Nephrol 15: 87.

21. Patel KP, Luo FJ, Plummer NS, Hostetter TH, Meyer TW (2012) The Production of p-Cresol Sulfate and Indoxyl Sulfate in Vegetarians Versus Omnivores. Clin J Am Soc Nephrol 7: 982-988.

22. Yamamoto S, Ito T, Sato M, Goto S, Kazama JJ, et,al (2019) Adsorption of Protein-Bound Uremic Toxins Using Activated Carbon through Direct Hemoperfusion in vitro. Blood Purif 48: 215-222.

23. Magnani S, Atti M (2021) Uremic Toxins and Blood Purification: A Review of Current Evidence and Future Perspectives.Toxins (Basel) 13: 246.

24. Tiranathanagul K, Khemnark N, Takkavatakarn K, et al. (2022) Comparative efficacy between hemodialysis using super high-flux dialyzer with hemoperfusion and high-volume postdilution online hemodiafiltration in removing protein bound and middle molecule uremic toxins: A cross-over randomized controlled trial. Artif Organs 46: 775-785.

25. Al Za'abi, Ali B, Al Toubi M (2013) HPLC-fluorescence method for measurement of the uremic toxin indoxyl sulfate in plasma. J Chromatogr Sci 51: 40-43.

26. Itoh Y, Ezawa A, Kikuchi K, Tsuruta Y, Niwa T (2013) Correlation between Serum Levels of Protein-Bound Uremic Toxins in Hemodialysis Patients Measured by LC/MS/MS. Mass Spectrom (Tokyo) 2.