Int J Clin Exp Med 2018;11(10):11198-11204
www.ijcem.com /ISSN:1940-5901/IJCEM0079151

Original Article

Effects of different blood purification techniques on interleukin-28 and mineral levels in patients

Hua Lu[1], Qingmin Wei[2], Gengxin Guo[1], Qian Liu[1], Jing Liu[1], Mingming Wang[1]

Departments of [1]Nephrology, [2]Cardiolgy, Xingtai People's Hospital Affiliated to Hebei Medical University, Xingtai 054000, Hebei, China

Received March 22, 2018; Accepted June 8, 2018; Epub October 15, 2018; Published October 30, 2018

Abstract: Objective: To investigate the effects of different combinations of blood purification techniques on interleukin-28 and mineral levels, and the effects of these combinations on the incidence of mineral and bone disorder (MBD) and inflammatory reaction in maintenance hemodialysis patients. Materials and methods: A total of 150 maintenance hemodialysis patients were divided into the hemodialysis group (HD group, n = 51), hemodialysis plus hemodiafiltration group (Group A, n = 56), and hemodialysis plus hemoperfusion group (Group B, n = 43). The changes of interleukin-28 (IL-28), calcium (Ca), phosphate (P), intact parathyroid hormone (IPTH), fibroblast growth factor 23 (FGF-23), β-cross-linked C-telopeptide of type 1 collagen (β-CTX), and procollagen type 1 N-terminal propeptide (P1NP) in three groups were evaluated. Results: The IL-28 and P levels were significantly increased in HD group after 6 months of treatment ($P < 0.05$). A significant decrease was found in IPTH levels in the Group A ($P < 0.05$), while a significant decrease in IL-28, IPTH, β-CTX, P1NP, and FGF-23 levels was noted in Group B ($P < 0.05$). IL-28, P, IPTH, β-CTX, P1NP, and FGF-23 levels in Group B were lower than that in HD group ($P < 0.05$). The number of patients with MBD and inflammatory reaction increased in the HD group. Conclusions: Hemodialysis plus hemodiafiltration is more effective than hemodialysis alone in the improvement of MBD and the inflammatory reaction; hemodialysis plus hemoperfusion has a stronger impact on the improvement of MBD.

Keywords: Hemodialysis, hemodiafiltration, hemoperfusion, IL-28

Introduction

Chronic kidney disease (CKD) is a manifestation of end-stage chronic renal failure. Uremia is characterized by metabolic disorders of vital components in the body. It may also induce disorders in multiple organ systems and even neurological dysfunction [1, 2]. In recent years, the incidence of CKD has been increasing [3]. Blood purification treatment, also known as hemodialysis, is currently the basic treatment to improve survival time of patients with uremia. Different purification methods can remove different substances [4, 5]. Blood purification includes plasma replacement, plasma exchange, hemodialysis (HD), hemodiafiltration (HDF), hemoperfusion (HP). Blood purification involves the removal of metabolites, residuals, and pathogenic substances transported in the blood through semi-permeable membrane diffusion, convection, selective filtration, or selective adsorption of a solid adsorbent that purifies the blood and corrects water-salt imbalances [6, 7].

However, the main side effect of maintenance hemodialysis are mineral and bone abnormalities (MBD) and bone events in patients, which are clinically manifested as changes in the composition and structure of bone tissue, hyperparathyroidism, abnormal metabolism of calcium and phosphorus, calcification of blood vessels, and soft tissues [8]. Bone mineral density (BMD) has a serious impact on the quality of life of patients. BMD also affects the prognosis and even leads to death of the patients.

Therefore, how to reduce the incidence of side effects such as bone events by different combinations of the existing blood purification technologies is a noteworthy issue. In this study, 150 maintenance hemodialysis patients undergoing different blood purification treatments were retrospectively analyzed to investigate the effects of different blood purification tech-

niques on bone events, minerals, and IL-28 levels.

Materials and methods

Subjects

Total of 150 patients who underwent maintenance hemodialysis in our hospital from February 2015 to February 2016 were retrospectively analyzed. The hemodialysis group (HD group, n = 51) included 32 male and 19 female patients (43.2 ± 21.3 years). The hemodialysis plus hemodiafiltration group (HD+HPF, Group A, n = 56) included 33 male and 23 female patients (46.1 ± 19.5 years) whereas the hemodialysis plus hemoperfusion group (HD+HP, Group B, n = 43) included 20 male and 23 female patients (44.5 ± 20.8 years). All the patients had undergone dialysis for more than six months; all patients were expected to survive more than one year; and all the patients had no cardiovascular or cerebrovascular events. The following patients were excluded from the study: minors; patients with a history of dialysis for more than ten years; patients with advanced cancer; patients with severe hematological disorders; and patients with severe bone disorders, such as osteoarthropathy, hereditary bone disease, osteonecrosis, bone tuberculosis, osteoarthritis syndrome, rheumatoid arthritis, and traumatic fractures. The study was approved by the Ethics Committee of Department of Nephrology, Xingtai People's Hospital Affiliated to Hebei Medical University. All the patients or their family signed the informed consent form.

Dialysis treatment methods

The following treatment methods and dialyzer protocols were applied.

For HDF dialysis, the German Fresenius Hemodialysis Machine (Shanghai Jieweifu Medical Devices Co., Ltd) was used once per week for Group A. Replacement fluid 5000 ml/h, blood flow 250-300 ml/min, dialysate flow 500 ml/min, dialysate calcium ion concentration 1.50 mmol/L, heparin sodium anticoagulation.

For HP dialysis, the HA130 Disposable Resin Hemoperfusion Device (Zhuhai Jafron Biomedical Co., Ltd) was used once per week for Group B. The adsorber was connected in series before the dialyzer, the capacity was 330 ml, the specific surface area was 600-1370 m^2/g, the blood flow rate was 180-220 ml/min, and heparin sodium was anticoagulated.

Test methods

Ca and P were measured using the Beckman-Olympus 5800 Automatic Biochemical Analyzer. IPTH was tested using the enzyme-linked immunosorbent assay (ELISA) provided by Shanghai Meixuan Biotechnology Co., Ltd in accordance with the operating manual's instructions. FGF-23 was tested by an ELISA kit (Shanghai Biotechwell Co., Ltd). B-CTX was detected by type I collagen carboxy-terminal peptide (CTx) ELISA kit (Shanghai Valan Biotech Co., Ltd.). PINP was detected using type I procollagen N-terminal propeptide (PINP) ELISA kit (Shanghai Westang Biotech Co., Ltd.). BMD was tested by digital dual-energy X-ray absorptiometry (EXA-3000, OsteoSys, Shanghai Co., Ltd.). The patients were divided into 3 groups according to the measured BMD: osteoporosis group, $T \leq -2.5$; osteopenia group, $-2.5 < T \leq -1$; normal group, $T > -1$.

Outcome measures

The effects of different combinations of dialysis methods on the inflammatory reaction and MBD in hemodialysis patients were evaluated by comparing changes in IL-28, Ca, P, IPTH, FGF-23, β-CTX, and P1NP levels between groups before and after 6 months of treatment.

Statistical analysis

All data was analyzed by SPSS version 19.0 software (Asia Analytics formerly SPSS China). Count data are expressed as rate and were compared with the Chi-square test. Continuous variables were presented as mean ± standard deviation (SD). Paired t-test was used to compare difference between pre- and post-treatment data. ANOVA analysis was performed to compare the difference among three different groups. A *P*-value < 0.05 was considered as statistically significant.

Results

Patient characteristics

Total of 150 patients with uremia were included in this study. No significant difference was

Table 1. Compare the basic data of the two groups

	HD group n = 51	A group n = 56	B group n = 43	Statistics	*P* value
Age	43.2 ± 21.3	46.1 ± 19.5	44.5 ± 20.8	0.269	0.765
Sex man (%)/woman (%)	32 (62.75)/19 (37.25)	33 (59.83)/23 (41.07)	20 (46.51)/23 (53.49)	2.690	0.261
Weight [n (%)]				3.388	0.184
< 60 Kg	39 (76.47)	35 (62.50)	26 (60.47)		
≥ 60 Kg	12 (23.53)	21 (37.50)	17 (39.53)		
Nation [n (%)]				2.574	0.276
Han	43 (84.31)	46 (82.14)	40 (93.02)		
Minority	8 (15.69)	10 (17.86)	3 (6.98)		
Residence [n (%)]				1.472	0.479
City	36 (70.59)	42 (75.00)	35 (81.40)		
Country	15 (29.41)	14 (25.00)	8 (18.60)		
Kt/V	1.26 ± 0.21	1.21 ± 0.23	1.28 ± 0.19	1.464	0.235
Dialysis ages (m)	71.21 ± 42.59	69.45 ± 41.87	72.64 ± 44.88	0.068	0.934
Hemoglobin (g/L)	94.78 ± 14.59	92.36 ± 14.31	96.74 ± 15.66	1.086	0.340

Table 2. Changes in IL-28 levels before and after treatment

Group	HD group (pg/mL)	A group (pg/mL)	B group (pg/mL)	F value	P
0 months	92.34 ± 12.58	95.68 ± 13.44	94.18 ± 11.94	0.919	0.401
6 months	72.47 ± 11.41	64.25 ± 12.55	57.69 ± 8.47	20.900	< 0.001
t	8.355	12.791	16.345		
P	< 0.001	< 0.001	< 0.001		

Table 3. Changes in mineral levels were found in 150 patients before and after treatment

		HD group	A group	B group	Statistics	*P* value
Ca	Pre	2.41 ± 0.51	2.29 ± 0.42	2.27 ± 0.39	1.433	0.242
	After	2.14 ± 0.46	2.09 ± 0.50	2.10 ± 0.34	0.183	0.833
	Statistics	0.624	1.115	1.041		
	P-value	0.623	0.048	0.087		
P	Pre	2.20 ± 0.99	2.38 ± 0.74	2.23 ± 0.47	0.720	0.489
	After	2.19 ± 0.60	2.01 ± 0.79	1.99 ± 1.11[a]	5.795	0.004
	Statistics	0.485	2.756	2.158		
	P-value	0.784	0.018	0.045		

Note: a: P < 0.05 compared with HD group.

found in general characteristics including sex, weight, and age among the three groups including HD group (n = 51), Group A (HD+HPF group, n = 56), and Group B (HD+HP group, n = 43) (**Table 1**).

Changes in IL-28 levels before and after treatment

IL-28 levels before and after 6 months of treatment of each group were: HD group (92.34 ± 12.58 pg/mL vs 72.47 ± 11.41 pg/mL); Group A (95.68 ± 13.44 pg/mL vs 64.25 ± 12.55 pg/mL); Group B (94.18 ± 11.94 pg/mL vs 57.69 ± 8.47 pg/mL). IL-28 levels were significantly improved after treatment (*t*-test, all P < 0.001). IL-28 levels after treatment in Group A and Group B were significantly better than those in the HD group (Analysis of variance, P < 0.001) (**Table 2**).

Changes of mineral levels in 150 patients before treatment and 6 months after treatment

We analyzed the changes in bone mineral levels before and after treatment in 150 patients. There was no difference in Ca and P levels between the three groups before treatment (P>0.05). After 6 months of treatment, the Ca and P levels in the three groups were changed. There was significant differences in Ca and P levels between the three groups after treatment (P < 0.05). Ca and P levels in group A and B after 6 months of treatment were significantly lower than before treatment (all P < 0.05), while in HD group, there was no significant difference in P levels after treatment (P>0.05) (**Table 3**).

Table 4. Changes of bone metabolism index in three groups

		HD group	A group	B group	Statistics	*P* value
IPTH	Pre	451.25 ± 45.33	431.58 ± 38.69	441.22 ± 58.79	2.282	0.106
	After	428.64 ± 40.19	401.22 ± 37.64[a]	382.69 ± 31.04[a,b]	52.977	< 0.001
	Statistics	3.301	2.231	5.613		
	P-value	0.008	0.041	0.003		
FGF-23	Pre	464.89 ± 93.98	464.37 ± 98.97	458.61 ± 95.28	0.060	0.942
	After	456.49 ± 100.47	401.47 ± 102.25[a]	385.18 ± 56.72[a]	14.116	< 0.001
	Statistics	0.537	2.112	2.869		
	P-value	0.715	0.046	0.016		
β-CTX	Pre	2.85 ± 1.60	2.89 ± 1.82	2.81 ± 1.03	0.110	0.896
	After	2.71 ± 1.14	2.54 ± 1.06	2.29 ± 1.26[a]	4.859	0.009
	Statistics	0.347	0.462	2.053		
	P-value	0.902	0.869	0.047		
PINP	Pre	154.55 ± 51.14	158.47 ± 31.22	154.69 ± 28.74	0.179	0.836
	After	149.29 ± 41.16	141.58 ± 37.34	132.58 ± 32.26[a]	19.714	< 0.001
	Statistics	0.347	1.032	2.217		
	P-value	0.902	0.237	0.043		

Note: a: P < 0.05 compared with HD group, b < 0.05 compared with group A.

Changes of bone metabolic indexes in 150 patients before treatment and 6 months after treatment

We analyzed some of the bone metabolic parameters in the three groups of patients. There was no difference in IPTH, FGF-23, β-CTX, and PINP between the three groups before treatment (P>0.05). After treatment, the IPTH levels in the three groups all decreased. P < 0.05). The levels of FGF-23 in A and B groups were decreased (P < 0.05), but there was no difference in FGF-23 levels in patients with HD (P>0.05). B-CTX and PINP was decreased (P < 0.05), but the levels of β-CTX and PINP were not statistically different between pre- and post-treatment in both HD group and A group (P>0.05). There were significant differences in IPTH, FGF-23, β-CTX, and PINP levels between the three groups after treatment (P < 0.05). Differences in IPTH levels between the two groups after 6 months of treatment were statistically significant (P < 0.05). The levels of FGF-23 in group A and B were lower than those in HD group (P < 0.05), but with no statistical difference between group A and B (P>0.05). β-CTX and PINP in group B was lower than that of group HD and group A (P < 0.05), but no difference between group A and group HD (P>0.05) (**Table 4**).

Incidence of bone events

After 6 months of treatment, there was only 1 new case of osteoporosis and osteopenia in the HD group, with no differences from before treatment. There were no new cases of osteopenia in Group A or Group B. Two patients with osteoporosis in Group A and 2 in Group B were cured. No significant differences were observed in overall incidence of bone events between the two groups (**Table 5**).

Discussion

With the prolonging of the dialysis period in patients with hemodialysis, bone formation and osteolysis becomes imbalanced, and the rate of bone turnover and osteoblast and osteoclast activities increase, resulting in abnormal bone resorption and mineralization and increased risks of MBD [9, 10]. Hip fracture may increase the mortality of hemodialysis patients. The 1-year survival rate of hemodialysis patients with hip fracture is reported to be below 40% [11]. Hence, how to reduce the incidence of side effects, such as bone events, using different combinations of existing blood purification technologies is an important issue.

In the present study, our results showed that improvements in IL-28 levels in the HD+HDF group and HD+HP group were better than those

Table 5. Incidence of bone events in three groups of patients

		HD group (n = 51)	A group (n = 56)	B group (n = 43)	Statistics	*P* value
Osteoporosis [n (%)]	Pre	15 (29.41)	13 (23.21)	9 (20.93)		
	After	16 (31.37)	11 (19.64)	7 (16.27)		
Low bone mass [n (%)]	Pre	20 (39.22)	21 (37.50)	20 (46.51)		
	After	21 (41.18)	25 (44.64)	24 (55.81)		
Bone mass normal [n (%)]	Pre	16 (31.37)	22 (39.29)	14 (32.56)		
	After	14 (27.45)	20 (35.71)	12 (27.91)		
The proportion of bone events (%, n)	Pre	68.63 (35)	60.71 (34)	67.44 (29)	0.856	0.652
	After	72.55 (37)	64.29 (36)	72.09 (31)	5.399	0.067
The increment rate of bone events (%, n)		3.92	3.58	4.65		

in HD group in maintenance hemodialysis patients. IL-28 exerts its defensive effects through the Janus kinase and activators of transcription pathway [12]. Arpaci D and colleagues [13] reported that IL-28 levels significantly increased in patients with Hashimoto's thyroiditis. Analysis of IL-28 gene polymorphisms found that the G allele may protect against Hashimoto's thyroiditis, which suggested that IL-28 was abnormally expressed in the inflammatory reaction. The inflammatory reaction is a significant problem for maintenance hemodialysis patients.

Due to the different methods and materials used by hemodialysis apparatus, there are differences observed in the clearance of substances using different blood purification techniques [14]. After 6 months of treatment, the clearance of Ca by hemodialysis was not significant, while changes in P levels were significant in Group B. The clearance of P in Group A was not significant, while it was significantly improved only in Group B. Although P is a small molecular substance, it often forms a complex with other macromolecular substances [15]. Therefore, clearance of P by HD is limited.

Although the level of IPTH was elevated after treatment in Group HD, the changes in the other mineral levels were not significant, indicating limited corrective effects of HD on mineral and bone disorder. The key to correcting mineral and bone disorders is to control hyperphosphatemia and secondary hyperparathyroidism [16]. A high-throughput dialyzer was used in HDF. The clearance of the medium molecular substance by HDF was satisfactory, which was very important for controlling hyperphosphatemia [17]. Our results also show that although the change of P levels in Group A was not significant, the level of P declined. It is unknown whether prolongation of treatment will increase the degree of such decline. In future studies, the observation period for P should be extended to investigate this issue. The results of this study also show that improvements in IPTH and FGF-23 in Group A were significant. It has been reported that use of generated dialysate in HDF improved the clearance rates of IPTH, FGF-23, and other substances and reduced the incidence of MBD [18]. The present study showed that the mineral clearing effects in Group B were better than those in Group A, demonstrating that the effects of HP were better than those of HDF. Such differences may be caused by differences in dialysis materials, research objects, etc. In this study, HD was combined with HDF, which also denoted an important difference. However, the results of this study suggested that the corrective effects of HD+HDF on mineral and bone disorder were more satisfactory. HD was also combined with HP. HP utilized selective adsorption of solid adsorbents to achieve the purpose of clearance. Our results show that clearance of Ca by HP was not significant, but clearance of P by HP was satisfactory. Comparison between the HP group and Group A showed improved corrective effects of HP on mineral and bone disorders. Furthermore, HD+HP has been shown to improve renal osteodystrophy [19]. However, changes in mineral content may be related to prognosis and mortality. Due to the short time frame in this study, this phenomenon could not be analyzed.

In summary, different combinations of hemodialysis techniques have different effects on

MBD in maintenance hemodialysis patients. The corrective effects of hemodialysis plus hemodiafiltration or hemoperfusion on MBD are better than those of hemodialysis alone; hemodialysis plus hemoperfusion has more advantages in improvement of bone metabolism markers. The results might be related to the short period and the small sample size of the study. These limitations should be corrected in future studies.

Acknowledgements

Hebei Xingtai City Science and Technology Project (No. 2015zz027-13).

Disclosure of conflict of interest

None.

Address correspondence to: Hua Lu, Department of Nephrology, Xingtai People's Hospital Affiliated to Hebei Medical University, No. 16, Hongxing Street, Xingtai 054000, Hebei, China. Tel: +86-156309-28200; E-mail: hualuhloo@163.com

References

[1] Yeung CK, Shen DD, Thummel KE, Himmelfarb J. Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport. Kidney Int 2014; 85: 522-528.

[2] Tonelli M, Karumanchi SA, Thadhani R. Epidemiology and mechanisms of uremia-related cardiovascular disease. Circulation 2016; 133: 518-536.

[3] Kaesler N, Magdeleyns E, Herfs M, Schettgen T, Brandenburg V, Fliser D, Vermeer C, Floege J, Schlieper G, Krüger T. Impaired vitamin K recycling in uremia is rescued by vitamin K supplementation. Kidney Int 2014; 86: 286-293.

[4] van Ballegooijen AJ, Zelnick L, Hoofnagle AN, Hamburg NM, Robinson-Cohen C, Roy-Chaudhury P, Cheung AK, Shiu YT, de Boer IH, Himmelfarb J, Beck G, Imrey PB, Kusek JW, Kestenbaum B; Hemodialysis Fistula Maturation (hfm) Study Group. Association of vitamin D metabolites with arterial function in the hemodialysis fistula maturation study. Am J Kidney Dis 2017; 69: 805-814.

[5] Sakaguchi Y, Fujii N, Shoji T, Hayashi T, Rakugi H, Isaka Y. Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis. Kidney Int 2014; 85: 174-181.

[6] Robinson BM, Zhang JY, Morgenstern H, Bradbury BD, Ng LJ, McCullough KP, Gillespie BW, Hakim R, Rayner H, Fort J, Akizawa T, Tentori F, Pisoni RL. Worldwide, mortality risk is high soon after initiation of hemodialysis. Kidney Int 2014; 85: 158-165.

[7] Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A; ESHOL Study Group. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol 2013; 24: 487-497.

[8] Soohoo M, Feng M, Obi Y, Streja E, Rhee CM, Lau WL, Wang J, Ravel VA, Brunelli S, Kovesdy CP, Kalantar-Zadeh K. Changes in markers of mineral and bone disorders and mortality in incident hemodialysis patients. Am J Nephrol 2016; 43: 85-96.

[9] Yin LL, Jing N, Zhao ZY, Liu XH, Du J, Qin LL, Song JG, Xu Y. Relationship between the gene polymorphism of osteoprotegerin and bone mineral density in hemodialysis patients. Eur Rev Med Pharmacol Sci 2017; 21: 37-41.

[10] Bossola M, Di Stasio E, Viola A, Leo A, Carlomagno G, Monteburini T, Cenerelli S, Santarelli S, Boggi R, Miggiano G, Vulpio C, Mele C, Tazza L. Dietary intake of trace elements, minerals, and vitamins of patients on chronic hemodialysis. Int Urol Nephrol 2014; 46: 809-815.

[11] Snit M, Gawlik R, Lacka-Gazdzik B, Kuzniewicz R, Dwornicki M, Owczarek A, Walaszczyk M, Grabiec P, Grzeszczak W. Substance P and intensity of pruritus in hemodialysis and peritoneal dialysis patients. Med Sci Monit 2013; 19: 723-732.

[12] Chiriac M, Gunther C, Becker C. Il-28-dependent activation of epithelial stat1 drives epithelial wound healing in inflammatory bowel disease. Gastroenterology 2017; 152: S90.

[13] Arpaci D, Celik SK, Can M, Cakmak Genc G, Kuzu F, Unal M, Bayraktaroglu T. Increased serum levels of IL-28 and IL-29 and the protective effect of IL28B rs8099917 polymorphism in patients with hashimoto's thyroiditis. Immunol Invest 2016; 45: 668-678.

[14] Brener ZZ, Bergman M. Necrotizing pancreatitis due to hypercalcemia in a hemodialysis patient with pica. Clin Kidney J 2014; 7: 399-401.

[15] Lau WL, Kalantar-Zadeh K. Why is the association of phosphorus and FGF23 with mortality stronger in african-american hemodialysis patients? Am J Nephrol 2015; 42: 22-24.

[16] Jiang JL, Ren W, Li Y, Liu GY, Zhou CP, Su KL, Chen W, Wang K, Ni LJ, Hu Z. The role of short daily hemodialysis in the control of hyperphosphatemia, secondary hyperparathyroidism and anemia. Int Urol Nephrol 2013; 45: 1725-1731.

[17] Wang M, You L, Li H, Lin Y, Zhang Z, Hao C, Chen J. Association of circulating fibroblast

growth factor-23 with renal phosphate excretion among hemodialysis patients with residual renal function. Clin J Am Soc Nephrol 2013; 8: 116-125.

[18] Vrdoljak I, Krbavcic IP, Bituh M, Vrdoljak T, Dujmić Z. Analysis of different thermal processing methods of foodstuffs to optimize protein, calcium, and phosphorus content for dialysis patients. J Ren Nutr 2015; 25: 308-315.

[19] Soohoo M, Feng ML, Obi Y, Streja E, Rhee CM, Lau WL, Wang J, Ravel VA, Brunelli S, Kovesdy CP, Kalantar-Zadeh K. Changes in markers of mineral and bone disorders and mortality in incident hemodialysis patients. Am J Nephrol 2016; 43: 85-96.