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Original Article

Comparison of combined blood purification techniques in treatment of dialysis patients with uraemic pruritus

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Abstract: Uremic pruritus affects many patients suffering from end-stage renal disease (ESRD) and has a negative impact on quality of life and survival. The aim of this study was to investigate the treatment effects of different combined blood purification techniques on uremic pruritus in ESRD patients. Forty maintenance hemodialysis patients with uremic pruritus were selected and randomly divided into combined treatment of hemodialysis with hemoperfusion group (HP+HD) and combined treatment of hemodiafiltration with hemoperfusion group (HP+HDF). Some relevant clinical parameters (age, gender, duration of dialysis, ESRD etiology, hemoglobin, albumin, and C-reactive protein) were evaluated. Blood urea nitrogen (BUN), creatinine, phosphate, parathyroid hormone (PTH) and β2-microglobulin were tested before and after treatment. A visual analogue scale (VAS) was used to assess the intensity of pruritus. The results showed that BUN, serum creatinine, phosphates, PTH and β2-microglobulin were significantly decreased after the therapy in the two groups ($P<0.05$). A more significant decrease ($P<0.05$) was observed in HP+HDF group as compared with HP+HD group. After 12 weeks of treatment, there were also significant differences in pruritus scores in HP+HD group and HP+HDF group. The pruritus remission rates in the HP+HD and HP+HDF groups were 75% and 100%, respectively. Therefore, our findings suggest a potential role for HP+HDF in the treatment of uremic pruritus.

Keywords: Uremia, pruritus, hemoperfusion, hemodialysis, hemodiafiltration

Introduction

Uremic pruritus is a common symptom in chronic hemodialysis patients and has a negative impact on quality of life and survival. Despite improvements in dialytic technology, the incidence of uremic pruritus is still tremendously high [1].

Previous studies have shown that xerosis, divalent ions, calcium-phosphate product, C-reactive protein, hepatitis, hyperparathyroidism, immune derangement, and opioid system alternation may be associated with uremic pruritus [2]. However, the mechanism of uremic pruritus is not yet fully understood. Common treatments used for uremic pruritus include antihistamines, steroids, emollients, charcoal, erythropoietin and ultraviolet phototherapy [3]. Unfortunately, because of insufficient understanding for uremic pruritus, the current treatment options are limited and unsatisfactory.

It is common experience that pruritus is more frequent in underdialysed patients and can be improved by increasing the efficacy of dialysis [4]. Previous study showed that the use of a high-flux dialyzer was associated with alleviation of pruritus intensity [2]. However, due to the low level of economic development, low-flux dialysis is the main means of extracorporeal blood purification therapy in China. Low-flux dialysis cannot remove the middle and large molecule uremic toxins and protein-bound toxins. As a result, the patients suffer from long-term complications and poor quality of life [5].

The main objective of this study was to compare the capabilities of combined treatments of hemoperfusion (HP) with hemodialysis (HD)

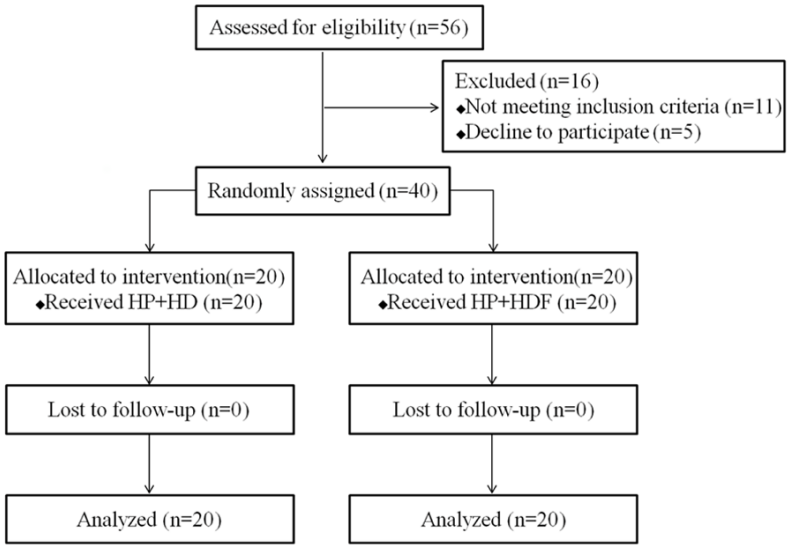

Figure 1. Flow chart of study participants.

and HP with hemodiafiltration (HDF) in clearing middle-molecule toxins and their effects on uremic pruritus.

Patients and methods

Patients

40 maintenance hemodialysis patients (30 males and 10 females) with pruritus in the hemodialysis center of the First Affiliated Hospital of Nanjing Medical University (Nanjing, China) were enrolled in the present prospective, randomized controlled study (**Figure 1**). Subjects were adults 18 years or older on stable hemodialysis for at least six months. Enrollment occurred between October 2013 and February 2014. Pruritus caused by other skin diseases or medication was excluded by careful clinical assessment. Patients with biliary atresia, liver problems, cancer, metabolic disorders or other diseases related to systemic pruritus were also excluded. This study was approved by the Institution Ethics Commission of Nanjing Medical University, written informed consents were obtained from all participants and the methods were carried out in accordance with the approved guidelines.

Blood purification methods

The procedure in the HP+HD group was conducted over 4 h. Two steps were involved during the HP+HD treatment: initially, the HA130-type resin HP (Jafron Biomedical Co., Ltd, Zhuhai, China) was connected in series prior to a high-flux dialyzer (Polyflux 14 L, Gambro) for the first 2 h. During this process, the blood flow rate was between 200 ml/min. For the next two hours, the blood went through the dialyzer alone and the blood flow rate was 250 ml/min. Bicarbonate dialysate was administered with a 500 ml/min flow rate and low-molecular-weight heparin served as the anticoagulant. The HP+HDF group was treated with a HA hemoperfusion cartridge (HA130, Jafron Biomedical Co., Ltd, Zhuhai, China) connected to the arterial end of a German Fresenius 4008S hemodialysis machine with an AV600 polysulfone filter. A hose, designed by our center, was used to connect the perfusion apparatus to the hemofilter, which was also served as an interface for the replacement fluid. Bicarbonate dialysis was conducted with low-molecular-weight heparin anticoagulant, dialysate flow of 500 mL/min, blood flow of 250 mL/min, and pre-dilution replacement fluid flow rate of 120 mL/min. The hemoperfusion cartridge was removed after 2 h of adsorption and saturation. Ultrafiltration of each patient depended on the clinical condition of the water balance. The low-molecular-weight heparin dose was adjusted according to clinical bleeding and clotting in the pipeline. All patients received combined blood purification treatments every 4 weeks for 12 weeks.

Blood samples and biochemical analysis

Blood samples were collected from the arterial blood line immediately prior to and following the RRT sessions. Blood routine tests were performed using an LH-750 Hematology Analyzer (Beckman Coulter, Inc., Fullerton, CA). The levels of blood urea nitrogen (BUN), serum creatinine, serum phosphate and albumin of the patients were measured using an Automatic Biochemical Analyzer (AU5400, Olympus Corporation, Tokyo, Japan). Changes in the levels of serum β2-microglobulin in patients were measured by the radioimmunoassay method. The kit used to detect β2-microglobulin was obtained from the American BioSource Com-

Table 1. Demographic and clinical characteristics of participants at baseline

Characteristic	HP+HD group (n=20)	HP+HDF group (n=20)	*P* value
Age (years)	66±16	59±18	0.193
Gender (% male)	75	75	0.715
Years of ESRD	8.75±5.76	8.30±5.82	0.807
ESRD etiology n (% total)			
Chronic glomerulonephritis	14 (70%)	13 (65%)	0.924
Diabetic nephropathy	2 (10%)	3 (15%)	
Hypertensive nephropathy	1 (5%)	2 (10%)	
Adult polycystic kidney disease	2 (10%)	1 (5%)	
Obstructive nephropathy	1 (5%)	1 (5%)	
Hemoglobin (g/dl)	103.28±15.43	109.50±14.69	0.211
Albumin (g/L)	37.69±3.79	38.42±4.10	0.602
C-reactive protein (mg/L)	4.51±2.33	3.49±1.27	0.245

Data are presented as mean ± SD.

pany (San Diego, CA, USA). Serum parathyroid hormone (iPTH) levels were measured using a UniCel DxI800 Access Immunoassay System (Beckman Coulter, Inc., Fullerton, CA).

Pruritus assessment

The severity of pruritus measured by the visual analogue scale (VAS) from 0 to 10 (0= no pruritus, 10= worst pruritus imaginable) was evaluated from each participant at baseline and follow-up according to a previous report [6]. Pruritus was scored before the initial dialysis and 12 week s after the dialysis.

Statistical analysis

The data were expressed as means ± standard deviation. Statistical analysis was performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Differences between two groups were compared using independent samples t test or Wilcoxon rank sum test for continuous variables and chi-squared or Fisher's Exact Test for categorical variables. The statistical significance of pre- and post-treatment differences was analyzed using paired t-tests. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics

There was no significant difference found regarding age, gender, duration of dialysis, ESRD etiology, hemoglobin, albumin, and C-reactive protein of patients in two groups (P< 0.05, **Table 1**).

Effect of dialysis on uremic toxins

As shown in **Table 2**, serum creatinine, BUN, phosphates, PTH and β2-microglobulin were found significantly decreased after the therapy in the two groups (P<0.05). A more significant decrease (P<0.05) was observed in HP+HDF group as compared with HP +HD group.

VAS assessment of itch severity

The impact of various combined blood purification techniques on uremic pruritus was explored in patients who self-reported itch intensity using a VAS score. After 12 weeks of treatment, HP+HD reduced itch from a mean VAS score of 8.06 (range, 6.8-9.32) to 5.03 (range, 3.73-6.33) and HP+HDF suppressed itch from a mean VAS score of 8.08 (range, 6.73-9.43) to 3.21 (range, 2.11-4.31), respectively (P<0.05, **Table 3**). Moreover, the pruritus remission rates in the HP+HD and HP+HDF groups were 75% and 100%, respectively (P<0.05, **Table 4**).

Discussion

It is well known that dialysis patients have a poor quality of life, in part because of a high symptom burden. Pruritus is a common and serious problem among hemodialysis patients. The significant effect of uremic pruritus on sleep, mood, and social functioning underscores the importance of efforts to improve treatment for this serious complication of ESRD [7]. The most consequential approaches to treatment are presented herewith: topical treatment, systemic treatment with μ-opioid receptor antagonists and κ-agonists, gabapentin, drugs with an anti-inflammatory action, ultraviolet phototherapy and acupuncture [8]. However, the efficacy of clinical treatment is usually poor. Previous study revealed that the development of severe uremic pruritus is associated with multiple clinical factors, including male gender, high pre-dialysis level of BUN, high lev-

Table 2. Changes in BUN, creatinine, phosphate, iPTH and β2-microglobulin before and after therapy

Treatment Groups	HP+HD group (n=20)		HP+HDF group (n=20)	
	Pretreatment	Decline (%)	Pretreatment	Decline (%)
BUN (mmol/L)	23.87±5.64	60.66±8.13*	23.81±8.09	76.21±6.53*,#
Creatinine (umol/L)	924.38±263.74	63.81±8.36*	954.51±274.98	75.31±8.53*,#
Phosphate (mmol/L)	1.84±0.50	45.63±8.13*	1.80±0.32	72.55±8.65*,#
iPTH (pg/ml)	443.66±255.78	20.31±10.06*	425.22±252.43	35.06±8.03*,#
β2-microglobulin (mg/L)	61.06±23.09	36.03±15.10*	60.98±20.55	63.06±16.05*,#

Data are presented as mean ± SD. Compared with the same group before dialysis, *P<0.05, compared with the HP+HD group, #P<0.05.

Table 3. Comparison of the pruritus scores

Treatment Groups	HP+HD group (n=20)		HP+HDF group (n=20)	
	Pretreatment	After 12 weeks	Pretreatment	After 12 weeks
VAS score	8.06±1.26	5.03±1.30*	8.08±1.35	3.21±1.10*,#

Data are presented as mean ± SD. Compared with the same group before dialysis, *P<0.05, 12 weeks after the initial dialysis, compared with the HP+HD group, #P<0.05.

Table 4. Comparison of the effects of treatment on pruritus

Treatment Groups	HP+HD group (n=20)	HP+HDF group (n=20)	*P* value
Complete remission (%, n)	60 (12)	75 (15)	
Partial remission (%, n)	15 (3)	25 (5)	
No remisson (%, n)	25 (5)	0 (0)	
Remission Rate (%)	75	100*	0.047

Compared with the HP+HD group, *P<0.05.

els of β2-microglobulin, calcium, phosphate and iPTH [9].

It was reported that pruritus increased before HD treatment and was relieved afterward, which is possibly explained by dialytic removal of causative molecules [10]. Previous study found that high BUN levels were a significant risk factor for severe uremic pruritus [9]. Our study showed that BUN levels decreased significantly after the combined blood purification therapy. However, the relationship between uremic pruritus and the doses of hemodialysis remains controversial. Some studies reported that achieving a higher Kt/V might reduce the degree of pruritus in hemodialysis patients [11, 12], while other study did not support this beneficial effect [13]. The international Dialysis Outcomes and Practice Patterns Study (DOPPS), large epidemiological studies, also showed that there was no significant relationship between increasing dialysis dose assessed as Kt/V values and the improvement of uraemic pruritus [14]. It should be recognized that Kt/V assesses dialysis efficacy by calculating the clearance of urea and cannot be used to evaluate the removal of middle molecular weight toxins, which are implicated in the pathogenesis of uremic pruritus.

Hyperparathyroidism is also related to uremic pruritus. Several studies have demonstrated that prompt relief of pruritus following parathyroidectomy or reduction of PTH levels by medical treatment [4]. Parathyroid hormone, a middle molecule with a molecular weight of 69000 D, is generally recognized as a major uremic toxin. During HD, dialysis membranes with a large pore size can remove PTH. But differences in plasma iPTH concentrations at the end of the dialysis session are subtle, since it will be compensated by homeostatic adaptations in glandular secretion [15]. Our present study showed that iPTH was dramatically cleared after HP+HD or HP+HDF therapy. However, there is still no clear-cut evidence that PTH is responsible for pruritus, since a contradictory report showed that serum levels of intact PTH did not correlate with the intensity of pruritus [16].

A high level of organic phosphates is related to pruritus and hyperparathyroidism [17]. The blood phosphorus concentration is the result of

protein catabolism and intake of protein-rich food [15]. Although phosphate is easily removed by HD, the clearance from the intracellular component is considerably less efficient [18]. We found that the phosphorus was effectively cleared after the usage of our combined blood purification techniques. In DOPPS study, serum phosphorus less than 3.5 mg/dl and within 5.5-6.7 mg/dl range accompanied the occurrence of pruritus with odds ratio of 1 and 1.2, respectively. When serum phosphorus level was higher than 6.7 mg/dl, the odds ratio increased to 1.37 [14]. Similar to Kt/V and iPTH, the results are also conflicting regarding phosphate and pruritus. Several other studies reported that there was no effect of phosphorus level on pruritus frequency [19, 20].

Although the precise pathophysiologic mechanisms of uremic pruritus with β2-microglobulin remain unclear, it has been recognized for many years that high β2-microglobulin levels are independently associated with the development of severe uraemic pruritus [9]. Compared with low-flux dialyzers, a high-flux dialyzer more efficiently removes middle molecules ranging in size from 1000 to 15000 Da. β2-microglobulin is a middle molecule with a molecular weight of 11800 Da. Previous study showed that low-flux dialyzers had a mean clearance of β2-microglobulin <10 ml/min during clinical dialysis [21], while several studies demonstrated that a single standard high-flux hemodialysis session reduces predialysis β2-microglobulin plasma levels to 50% [22]. However, in China and in other developing countries, low-flux dialysis is still the main method for toxin clearance, and it cannot remove the middle-molecule uremic toxins. Our results found that post-dialysis β2-microglobulin levels clearly decreased to 64% in HP+HD group and 37% in HP+HDF group respectively. The clearance of β2-microglobulin was very effective after the combination of HP and HDF therapy.

Hemoperfusion is a most often used process to treat poisoning, as it can clear macromolecular toxins via adsorption to a large surface area of activated charcoal or polymer resin [23]. Previous studies used a commercial connecting pipeline to connect the HA hemoperfusion cartridge to the filter, and the post-dilution HDF was adopted in which the replacement fluid is infused downstream of the dialyser [24, 25]. The high ultrafiltration rates used in post-dilution HDF possibly resulted in clotting of the extracorporeal circuit. In present study, our center designed a hose to connect the perfusion apparatus to the hemofilter. This hose was used as an interface for the replacement fluid, which managed to achieve the pre-dilution HDF. The combination of HP and pre-dilution HDF mode allows effective purification of different molecular weight toxins.

The treatment of uremic pruritus remains a frustrating endeavor and continues to present a significant therapeutic challenge for clinicians. The data from this study of the efficacy of two different combination therapies used for treating hemodialysis patients with uremic pruritus show significant improvement of serum creatinine, BUN, phosphates, iPTH and β2-microglobulin in both HP+HD and HP+HDF group. A more significant decrease of these toxins was observed in HP+HDF group as compared with HP+HD group. Besides, pruritus relief and remission rate were more remarkable in HP+HDF group compared with HP+HD group, indicating that HP+HDF was an effective blood purification therapy for removing toxins and alleviating uremic pruritus.

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Disclosure of conflict of interest

None.

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