Renal Replacement Therapy

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Efficacy of polymethylmethacrylate membrane hemodiafilter Filtryzer® PMF™-21A in improving pruritus in hemodialysis patients: a prospective interventional study

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Abstract

Background Hemodialysis-associated pruritus (HAP) occurs in 60–80% of hemodialysis patients. This significant complication not only decreases quality of life through sleep disturbance and depression, but also leads to poor survival outcomes. The polymethylmethacrylate (PMMA) membrane was the first synthetic polymer membrane for the hollow-fiber artificial kidney created in 1977. PMMA membrane dialyzers have been reported to be effective for improving various complaints, including pruritus, and nutritional status. In Japan, a PMMA membrane hemodiafilter Filtryzer® PMF™-A (PMF-A) was launched in November 2021 and subsequently became available for online hemodiafiltration (OHDF). This study aimed to determine whether PMF-A effectively improves pruritus in hemodialysis patients.

Methods Participants were 20 patients (median age 74.5 years) on predilution OHDF (pre-OHDF) or postdilution OHDF (post-OHDF) using an Asymmetric Triacetate Membrane® hemodiafilter (FIX-210E eco or FIX-210S eco), who were experiencing pruritus of "very mild" or higher severity based on the Shiratori severity score either during the daytime or nighttime. After switching to post-OHDF with PMF-21A (substitution flow rate: 10 L/session), the substitution flow rate was gradually increased according to results of pruritus evaluation every 2 weeks over 3 months. The primary endpoint was the severity of pruritus evaluated using visual analogue scale (VAS) and the Shiratori severity score. Secondary endpoints included white blood cell count (WBC), hemoglobin level (Hb), platelet count (Plt), serum albumin level (Alb), high-sensitivity C-reactive protein (hsCRP), IL-6, dry weight (DW), and solute removal performance.

Results The median VAS score was significantly decreased 2 weeks after switching compared with baseline (44 mm) and remained significantly decreased at Week 12 (22 mm; $p < 0.01$). From baseline to Week 12, 16 patients (80%) showed improvement in VAS score. The percentage of patients with mild to moderate daytime pruritus according to the Shiratori severity score decreased significantly from 80.0% to 45.0% ($p < 0.05$), whereas no significant change was observed for nighttime pruritus ($p = 0.267$). Pre-dialysis serum β_2-MG levels were significantly higher at Week 12 compared with baseline. No significant changes were observed in WBC, Hb, Plt, serum Alb, hsCRP, IL-6, or DW.

Conclusions OHDF with PMF-21A may be more effective in improving HAP.

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Keywords Hemodialysis-associated pruritus, Polymethylmethacrylate, Filtryzer®PMF™-A, Online hemodiafiltration, Visual analogue scale, Shiratori severity score

Background

Hemodialysis-associated pruritus (HAP) is observed in 60–80% of hemodialysis patients and is a significant complication that not only decreases the quality of life through sleep disturbance and depression, but also leads to poor survival outcomes [1–10].

Pruritus is classified as peripheral (cutaneous), central, neuropathic, and psychogenic. The main mechanisms of peripheral (cutaneous) pruritus include accumulation of pruritogens such as medium-to-high molecular weight substances, calcium, and phosphorus; excessive production of itch mediators such as histamine, substance P, and various inflammatory cytokines; and increased sensitivity to external stimuli due to dry skin, C-fiber elongation in the skin, decreased itch threshold, and skin hypersensitivity [11–14]. Central pruritus is associated with abnormal itch control within the central nervous system due to an abnormal endogenous opioid balance in the dorsal horn of the spinal cord and thalamus [15–17], astrocyte activation in the dorsal horn of the spinal cord [18], and other factors. The causes of neuropathic pruritus include abnormal excitation and hypersensitivity at sites of nerve damage/repair mediated by glutamic acid, substance P, and calcitonin gene-related peptide [19], while those of psychogenic pruritus include stress and depression [20].

HAP is often refractory to treatment, likely due to the combined involvement of more than one of the above mechanisms, and requires cause-specific and comprehensive treatment [10, 21–25]. Accumulation of pruritogenic medium to high molecular weight substances is a particularly important factor [26–29], and these substances should be actively eliminated by blood purification therapy.

The polymethylmethacrylate (PMMA) membrane was the world's first synthetic polymer membrane for the hollow-fiber artificial kidney created in 1977. This membrane is highly biocompatible because it does not contain polyvinylpyrrolidone (PVP), a hydrophilic agent, or bisphenol A (BPA), which is derived from certain raw materials, and may inhibit the production of inflammatory cytokines. The membrane also has protein adsorption properties, even absorbing high molecular weight proteins such as β_2-microglobulin (β_2-MG), interleukin-6 (IL-6), tumor necrosis factor-α, and soluble CD40 ligand, while it exhibits excellent permeability to high molecular weight substances of size equivalent to or larger than albumin. PMMA membrane dialyzers have been reported to be effective for improving various complaints, including pruritus, and nutritional status [30–39]. In Japan, a PMMA membrane hemodiafilter, Filtryzer® PMF™-A (PMF-A), was launched in November 2021 and has since become available for use in online hemodiafiltration (OHDF).

The aim of this study was to determine whether the use of PMF-A in OHDF would be effective for improving pruritus in hemodialysis patients.

Methods

Patients

This study involved 20 patients (14 male and 6 female) on predilution OHDF (pre-OHDF) or postdilution OHDF (post-OHDF) using an Asymmetric Triacetate (ATA) Membrane® hemodiafilter (FIX-210E eco or FIX-210S eco) who were experiencing pruritus of "very mild" or higher severity based on the Shiratori severity score either during the daytime or nighttime. Median [interquartile range (IQR)] age was 74.5 [64.5, 84.0] years and median [IQR] duration of dialysis was 5.0 [1.0, 9.3] years. Primary diseases included diabetes (n = 13), chronic glomerulonephritis (n = 3), nephrosclerosis (n = 2), and unknown (n = 2). The reason for selecting the ATA Membrane® hemodiafilter was to continue eliminating the effects of PVP and BPA on pruritus after the study began.

Study design

This study was a single-center, single-group, prospective, minimally invasive interventional study. Patients were switched from pre-OHDF or post-OHDF with FIX-210E eco or FIX-210S eco to post-OHDF with PMF-21A. The treatment conditions before the switch are shown in Table 1. The substitution flow rate was initially set at 10 L/session, and if there was no improvement in pruritus at pruritus assessments every 2 weeks, the rate was increased in increments of 2 L/session over a period of 3 months (Fig. 1). The substitution flow rate could be increased up to 20 L/session but was decreased if the serum albumin level (Alb) decreased below 3.0 g/dL. The upper limit of transmembrane pressure was set at 200 mmHg. The treatment time, number of dialysis sessions per week, blood flow rate, and dialysate flow rate were kept unchanged in principle. Although pre-existing antipruritic treatments were not changed in principle, dose reduction or discontinuation of antipruritic treatment was allowed if the pruritus improved.

Table 1 Treatment conditions before the switch to PMF-21A

	FIX-210E eco (n = 9)	FIX-210S eco (n = 11)
Dilution mode, n		
Pre	7	7
Post	2	4
Substitution flow rate, L/session (mean ± SD)		
Pre	51.4 ± 8.4	49.7 ± 4.2
Post	12.3 ± 1.8	13.0 ± 2.2
Blood flow rate, mL/min (mean ± SD)	270 ± 29	280 ± 47
Total dialysate flow rate, mL/min	500	500
Dialysis frequency, sessions/week	3	3
Dialysis time, h	4	4

PMF-21A Filtryzer® PMF™-A, *SD* standard deviation

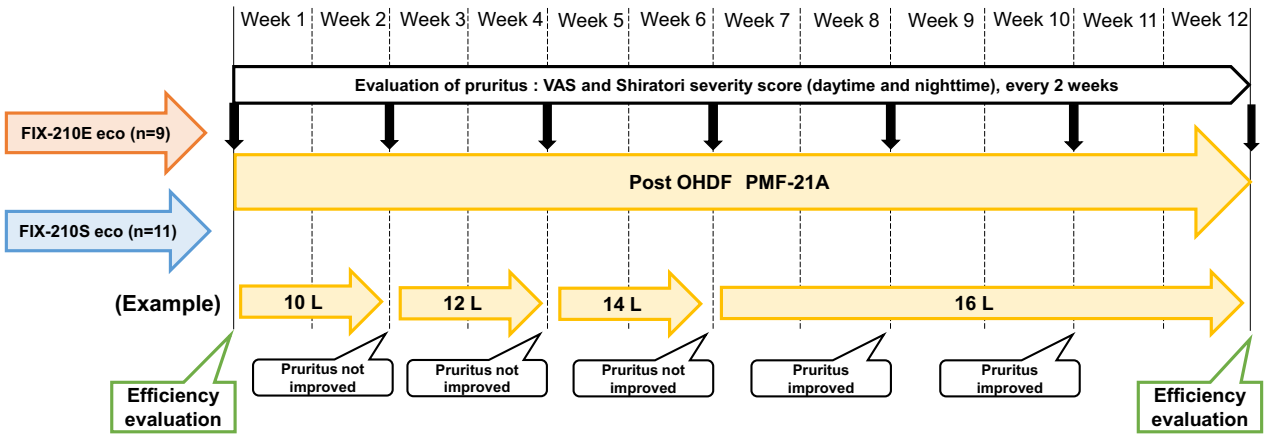

Fig. 1 Protocol for changing treatment conditions. *OHDF* online hemodiafiltration; *PMF-21A* Filtryzer® PMF™-A

The primary endpoint was severity of pruritus as assessed by the visual analogue scale (VAS) [40–43] and the Shiratori severity score [44], as well as the percentage of patients using antipruritic treatments. Secondary endpoints included blood parameters (white blood cells [WBC], hemoglobin [Hb], and platelets [Plt]) and inflammation markers (high-sensitivity C-reactive protein [hsCRP] and IL-6). Serum Alb, serum corrected calcium (Ca), serum inorganic phosphorus (IP), serum whole parathyroid hormone (whole PTH), dry weight (DW), and pre-dialysis serum β_2-MG levels were also measured. To determine removal efficiency, the removal rates and amounts of blood urea nitrogen (BUN), creatinine (Cr), IP, β_2-MG, and α_1-microglobulin (α_1-MG), and albumin leakage were measured before (baseline) and 12 weeks after the switch (Week 12).

For β_2-MG and α_1-MG, adsorption clearance, defined as the difference between blood-side clearance (C_{LB}) and dialysate-side clearance (C_{LD}) (C_{LB}–C_{LD} [mL/min]) [45], was calculated at 15, 60, 120 and 240 min into treatment to evaluate adsorption capacity. C_{LB} (1) and C_{LD} (2) were calculated using the following formulas, and the difference between them, that is, Eq. (1) minus Eq. (2), was calculated as the adsorption clearance.

$$C_{LB} = \frac{C_{Bi} - C_{Bo}}{C_{Bi}} \times Q_B(\mathrm{mL/min}) \quad (1)$$

$$C_{LD} = \frac{C_{Do}}{C_{Bi}} \times Q_D(\mathrm{mL/min}) \quad (2)$$

Here, C_{Bi} is the concentration at the hemodiafilter blood inlet [mg/mL], C_{Do}, is the concentration at the hemodiafilter dialysate outlet [mg/mL], Q_B is the blood flow rate, and Q_D is the dialysate flow rate.

Evaluation of pruritus

The severity of pruritus, the primary endpoint, was evaluated using the VAS and Shiratori severity score. The VAS consisted of a horizontal line with "no pruritus (0 mm)" at the left end and "worst possible pruritus (100 mm)" at the right end, on which the patients drew a vertical line indicating the severity of the most intense pruritus they had recently experienced. The distance from the left end to the vertical line (mm) was determined.

The severity of pruritus based on the Shiratori severity score was evaluated separately for daytime and nighttime pruritus. Daytime pruritus was evaluated on the following 5-point scale: 0="No itching at all" (no symptoms), 1="Tolerable without scratching" (very mild), 2="Subsides after light scratching" (mild), 3="Subsides after considerable scratching" (moderate), and 4="Does not subside, prompting repeated scratching" (severe). Nighttime pruritus was evaluated on the following 5-point scale: 0="No itching at all" (no symptoms), 1="Slight itching at bedtime, but not to the extent that I consciously scratch; I sleep well" (very mild), 2="Some itching, but subsides after scratching; I don't wake up due to itchiness" (mild), 3="I wake up due to itching; I can fall asleep after scratching once but unconsciously scratch while asleep" (moderate), and 4="I can hardly sleep due to itching; I constantly scratch, but it makes me itchier" (severe).

Changes over time were investigated in the numbers of patients using moisturizers, topical steroids, other topical drugs, oral antihistamines, nalfurafine hydrochloride, and gamma-aminobutyric acid (GABA) receptor agonists for the treatment of pruritus.

Statistical analysis

Statistical analysis was performed using the Jonckheere–Terpstra test, Cochran–Armitage test, Friedman test, Wilcoxon signed rank sum test, and paired-t test, with a significance level of < 5%. All statistical analyses were performed using SPSS version 25.0 for Windows (IBM Japan, Inc., Tokyo, Japan).

Ethical approval

This study was approved by the Ethical Review Committee of Tsuchiya General Hospital (Approval No. E220328-5) and was conducted in accordance with the principles of the Declaration of Helsinki. After obtaining prior verbal consent from each patient enrolled in the study, informed consent was documented in writing in their medical record.

Results

Changes in pruritus

The median VAS score significantly decreased in 2 weeks after the switch compared with baseline (44 mm) and remained significantly decreased at Week 12 (22 mm; $p < 0.01$; Fig. 2). Looking at the individual changes in VAS score from baseline to Week 12, 16 patients had a decrease in VAS score, meaning that 80% of patients had improvement in pruritus. Two patients had an increase in VAS score, but by less than 10 mm (from 20 to 28 mm and from 14 to 23 mm, respectively; Fig. 3).

According to the Shiratori severity score, no patient had severe pruritus from baseline through Week 12, and the percentage of patients with mild to moderate daytime pruritus decreased significantly from 80.0 to 45.0% ($p < 0.05$), but there was no significant change in nighttime pruritus ($p = 0.267$; Figs. 4 and 5).

Change in use of antipruritic treatments

The number of patients using moisturizers was 14 (70.0%) at baseline and 13 (65.5%) at Week 12 ($p = 0.669$). Topical steroids were used by 13 patients (65.0%) at baseline and 11 (55.0%) at Week 12 ($p = 0.477$). The number of patients using other topical drugs was 2 (10.0%) at baseline and 2 (10.0%) at Week 12 ($p > 0.999$). Oral antihistamines were used by 4 patients (20.0%) at baseline and 3 (15.0%) at Week 12 ($p = 0.599$). The number of patients using nalfurafine hydrochloride was 6 (30.0%) at baseline and 5 (25.0%) at Week 12 ($p = 0.823$). GABA receptor agonists were used by 2 patients (10.0%) at baseline and 3 (15.0%) at Week 12 ($p = 0.635$). There were no significant changes over time in the percentage of patients using antipruritic treatments.

Changes in primary and secondary endpoints

The median [IQR] pre-dialysis serum β_2-MG level was significantly higher at Week 12 (27.2 [21.8, 28.9] mg/L) compared with baseline (25.1 [19.7, 27.6] mg/L; $p < 0.05$). No significant changes were observed in other variables (WBC, Hb, Plt, serum Alb, corrected Ca, IP, whole PTH, hsCRP, IL-6, and DW; Table 2).

Removal efficiency

Removal efficiency was compared in two groups: patients who switched from FIX-210E eco to PMF-21A (group A) and those who switched from FIX-210S eco to PMF-21A (group B (Tables 3, 4). The mean (± standard deviation) substitution flow rate with PMF-21A at Week 12 was 14.8 ± 2.0 L/session for group A and 15.1 ± 2.2 L/session for group B. No significant differences were observed in the removal rate and amount of low molecular weight solutes (i.e., BUN, Cr, and IP). For β_2-MG and α_1-MG, the removal rate and the removal amount on the effluent side were significantly lower with PMF-21A. Albumin leakage was also significantly lower with PMF-21A.

Patients were divided into an improvement group with the 16 patients whose VAS score decreased and a

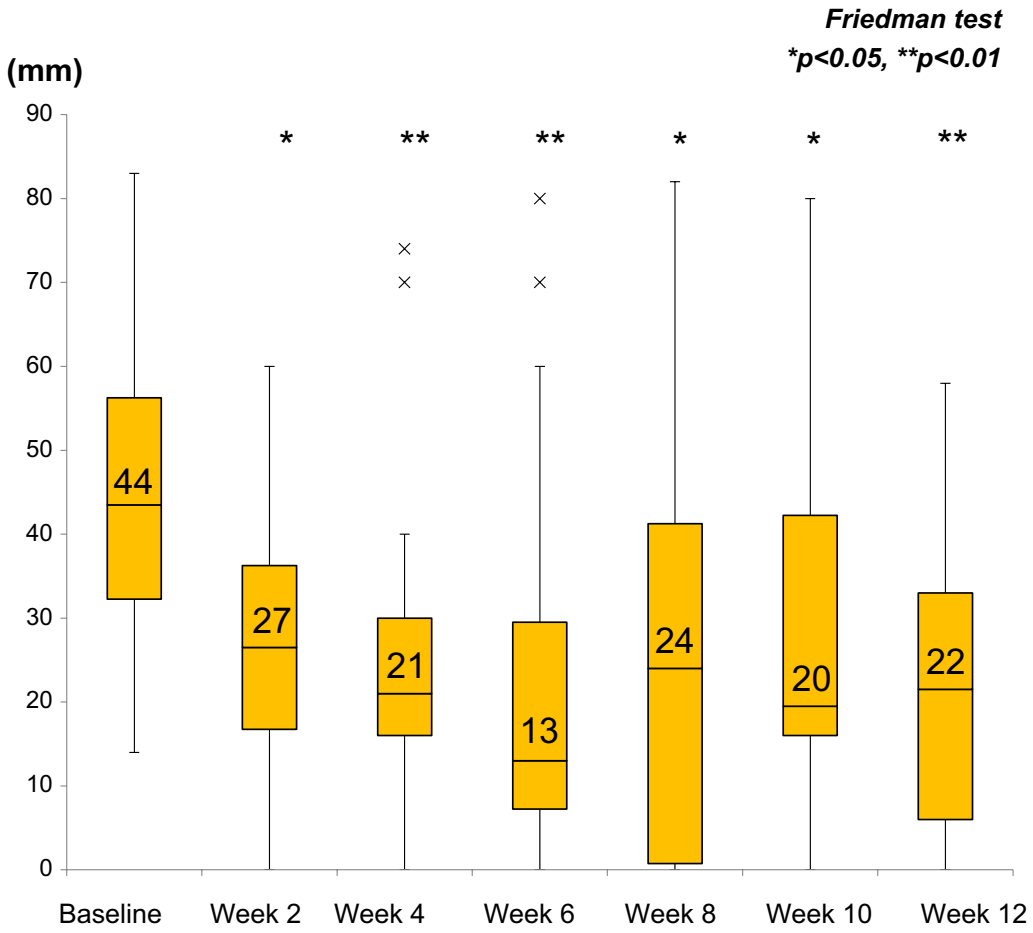

Fig. 2 Change over time in median visual analogue scale (VAS) score (n = 20)

non-improvement group with the 4 patients whose VAS score was unchanged or increased at Week 12, and the substitution flow rate (mean ± standard deviation) and removal rates of β_2-MG and α_1-MG (means ± standard deviations) were compared between the groups. The substitution flow rate at Week 12 was larger in the non-improvement group (16.5 ± 1.7 L/session) than in the improvement group (14.5 ± 1.9 L/session), although the difference between the groups was not significant ($p = 0.088$). The removal rates of β_2-MG at baseline and Week 12 were 76.7 ± 5.6% and 70.5 ± 6.9%, respectively, in the improvement group, and 75.9 ± 5.0% and 69.4 ± 4.2%, respectively, in the non-improvement group: the removal rate was decreased at Week 12 compared with baseline in both groups. The removal rates of α_1-MG at baseline and Week 12 were 28.0 ± 7.4% and 17.5 ± 5.1%, respectively, in the improvement group, while 30.4 ± 9.9% and 14.6 ± 2.9%, respectively, in the non-improvement group: the removal rate was decreased at Week 12 compared with baseline in both groups. The removal rates of β_2-MG and α_1-MG at Week 12 were not significantly different between the groups ($p = 0.779$ and $p = 0.325$, respectively).

Adsorption clearance

Adsorption clearance was evaluated for 6 of the 11 patients who switched from FIX-210S eco to PMF-21A and were matched for treatment conditions other than dilution mode and substitution flow rate. Comparisons were made under the following conditions: treatment time of 4 h, blood flow rate of 250 mL/min, total dialysate flow rate of 500 mL/min, and substitution flow rate of 48 L/session for pre-OHDF with FiX-210S eco and 14 L/session for post-OHDF with PMF-21A session.

With FIX-210S eco, the C_{LB} and C_{LD} for both β_2-MG and α_1-MG were almost identical from 15 min to 4 h after the start of treatment, giving no adsorption clearance (Fig. 6). In contrast, with PMF-21A, there were differences between C_{LB} and C_{LD} for both β_2-MG and α_1-MG, giving adsorption clearance of 83.9 ± 6.5 mL/min

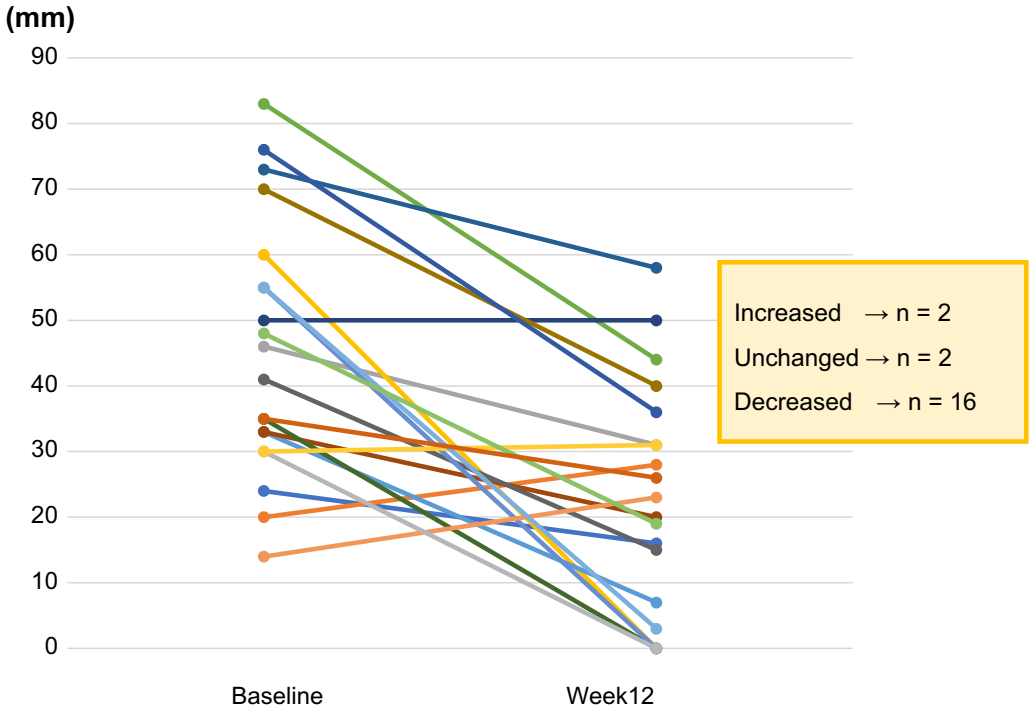

Fig. 3 Individual changes in visual analogue scale (VAS) score (n = 20)

at 15 min, 72.2 ± 5.5 mL/min at 60 min, 63.4 ± 3.3 mL/min at 120 min, and 52.8 ± 5.2 mL/min at 240 min for β_2-MG; and 6.9 ± 1.2 mL/min at 15 min, 6.3 ± 1.3 mL/min at 60 min, 6.0 ± 1.0 mL/min at 120 min, and 5.5 ± 1.1 mL/min at 240 min for α_1-MG. The adsorption clearance of PMF-21A showed a decreasing trend over time but was maintained even at the end of treatment.

Discussion

PMMA membrane hemodiafilters are characterized by adsorption due to the occlusion of protein molecules into pores of the homogeneous membrane structure, and are capable of removing high molecular weight substances that cannot be removed by permeation (diffusion and filtration), such as protein-bound uremic toxins. It also has a low complement activation potential and uses the same membrane surface modification technology as Filtriser NF® [36, 37] to both adsorb proteins and inhibit platelet adhesion, resulting in good biocompatibility. Its pore size is designed to be small, which can reduce albumin leakage. The homogeneous membrane structure and protein adsorption properties make the membrane less permeable than the polysulfone (PS) membrane and produce a lower ultrafiltration rate (UFR), making it unsuitable for high-volume pre-OHDF, as it is often associated with increased transmembrane pressure. However, it can be used under normal conditions in the postdilution mode. The PMMA membrane also has broad fractionation ranges; although its β_2-MG removal performance is inferior to that of the PS membrane, it is capable of reducing amino acid leakage and removing high molecular weight substances.

Several centers have reported the following findings supporting the performance and usefulness of PMMA membrane hemodiafilters: (1) β_2-MG and α_1-MG are rarely detected in the dialysate and are removed mainly by adsorption; (2) there is no excessive albumin leakage in both pre- and post-OHDF and albumin leakage is kept low, ensuring safety; and (3) it is effective in improving complaints including pruritus and maintaining peripheral circulation during dialysis. Given these reports, we also examined whether the use of PMMA membrane hemodiafilters in post-OHDF improves pruritus in our hemodialysis patients.

The median VAS score at Week 12 was lower than that at baseline in 16 patients (80%), indicating improvement in pruritus. The proportion of patients with mild to moderate pruritus according to the Shiratori severity score decreased significantly for daytime pruritus, but not for nighttime pruritus. There were more patients with no or very mild pruritus at baseline, and fewer patients with mild and moderate pruritus at baseline during the nighttime than during the daytime. This may be a reason why

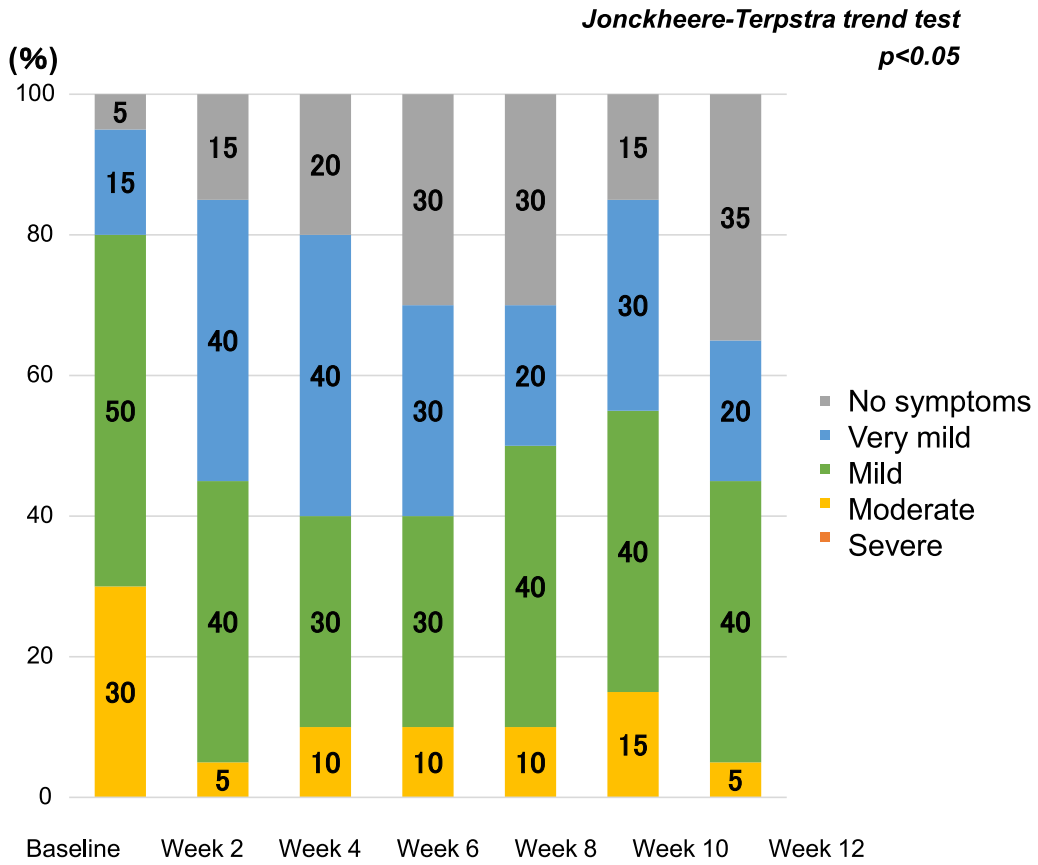

Fig. 4 Changes in Shiratori severity score for daytime pruritus (n = 20)

there was no significant difference in nighttime pruritus after the switch.

To improve pruritus in hemodialysis patients on OHDF, it is important to actively remove pruritogenic medium to high molecular weight substances by high-volume pre-OHDF or post-OHDF. β_2-MG (molecular weight, 11,800 Da) was shown to be a pruritogen in experiments using mice [46, 47], and may cause pruritus in humans as well. Furthermore, α_1-MG (MW 33,000 Da) has been used as a surrogate marker for the removal of high molecular weight uremic toxins, and efficient removal of α_1-MG has been associated with improved pruritus [48–50]. Recently, α_1-MG has attracted attention for its antioxidant activity as a potent radical scavenger against oxidative stress caused by reactive oxygen species, and active removal of α_1-MG is thought to not only result in the removal of uremic toxins in the molecular weight range of α_1-MG, but also promote the turnover of α_1-MG and its antioxidant action as a radical scavenger [18, 51–55]. Thus, to improve pruritus, the target values for treatment efficiency parameters should be set as follows: β_2-MG removal rate of 80% or higher, and α_1-MG removal rate of 30–40% (3 g albumin leakage). For refractory pruritus, an α_1-MG removal rate of 40% or higher (albumin leakage of 5 g or higher) should be targeted [48–50, 56], and the use of hemodiafilters that do not contain pruritogenic substances, such as PVP and BPA, should also be considered [56].

In this study, 80% of patients had improvement in pruritus even though PMF-21A had lower removal rates of β_2-MG and α_1-MG compared with ATA Membrane® hemodiafilters. Also, the removal rates of β_2-MG and α_1-MG were decreased at Week 12 compared with baseline in both the group with and the group without improvement in pruritus, and there was no significant difference in the removal rates between the groups. Thus, the mechanism for improvement of pruritus by use of PMF-21A cannot be explained by the efficiency of β_2-MG and α_1-MG removal. Aoike et al. showed that the mechanism by which PMMA membrane dialyzers improve pruritus is that the PMMA membranes adsorb substances in a broader molecular weight range than PS membranes. They found a substance (not IgG) with a molecular weight similar to that of IgG (molecular weight, 160,000 Da) in the plasma of dialysis patients with pruritus that induced

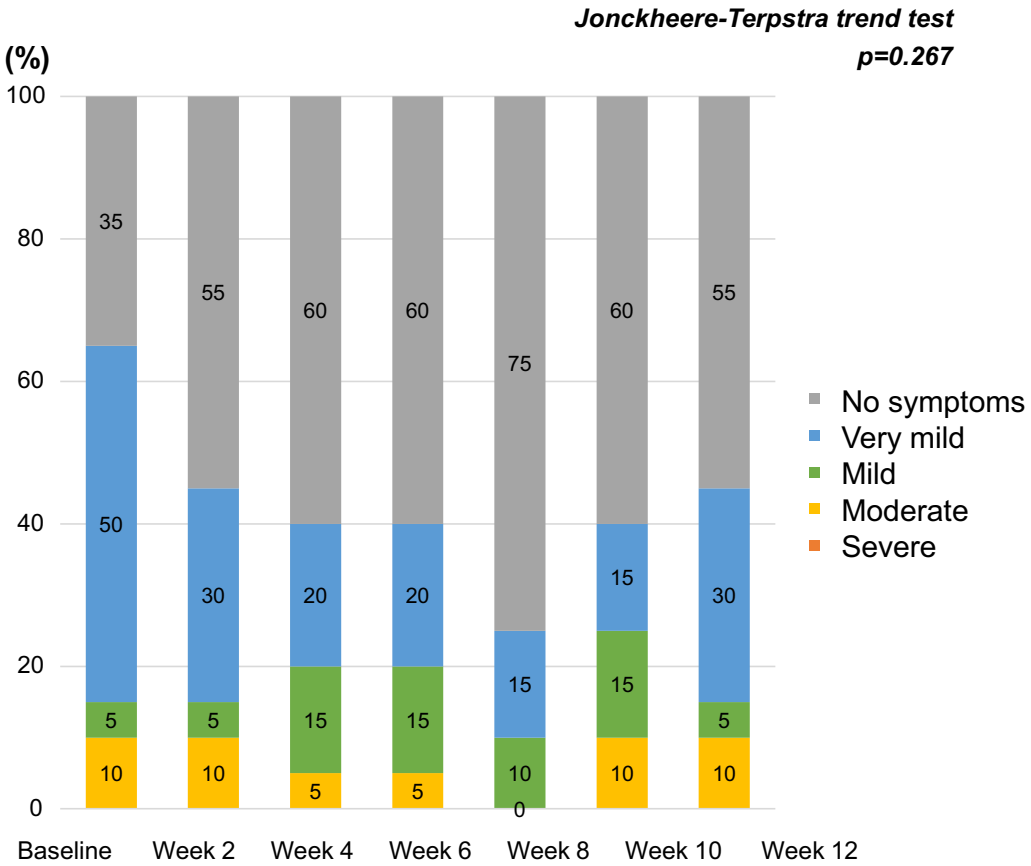

Fig. 5 Changes in Shiratori severity score for nighttime pruritus (n = 20)

degranulation of rat mast cells (i.e., histamine release from the cells). They also found that degranulation did not occur when a solution containing this substance was exposed to a PMMA membrane dialyzer in vitro, indicating that a PMMA membrane dialyzer adsorbed this substance [33]. Although uncertain, a similar mechanism involving adsorptive removal of high molecular weight pruritogens may explain the improvement in pruritus with the use of PMF-21A.

Although β_2-MG itself can be a pruritogen, the adsorption clearance for β_2-MG and α_1-MG was calculated to evaluate the adsorption capacity of PMF-21A for medium to high molecular weight substances. We found that β_2-MG and α_1-MG were removed when PMF-21A but not ATA Membrane® hemodiafilters were used, confirming adsorptive removal of these substances. Thus, we inferred that pruritogens were removed by adsorption to PMF-21A, resulting in improvement in pruritus. However, we examined adsorption clearance of these substances only, and whether PMF-21A can remove possible pruritogens with a higher molecular weight needs to be investigated.

Albumin leakage was lower with PMF-21A compared with ATA Membrane® hemodiafilters. Given that high-volume pre-OHDF and post-OHDF are associated with high albumin leakage, PMF-21A with low albumin leakage may be suitable for improving pruritus in undernourished or elderly patients with low serum Alb levels.

While improvement in pruritus was observed, an increase in serum β_2-MG levels was observed at Week 12. This was likely due to decreased removal of β_2-MG rather than increased production of β_2-MG, given the significantly lower β_2-MG removal rate of PMF-21A compared with ATA Membrane® hemodiafilters. Serum β_2-MG levels have been suggested to be a prognostic factor and high serum β_2-MG levels have been correlated with cardiovascular disease mortality and all-cause mortality [57, 58]. This suggests the need to monitor the change in serum β_2-MG levels over time.

This study has several limitations. The first is the small sample size due to the single-center study design. The second is the single-group design without a control group, which precludes us from proving that PMF-21A was the most important factor for the improvement of HAP. Third, the study did not adequately evaluate the adsorption capacity of PMF-21A for pruritogenic high molecular weight substances, which is one of the

Table 2 Changes over time in secondary endpoints (n = 20)

	Baseline	Week 4	Week 8	Week 12	*p* value
WBC, /μL	5295 [4462.5, 7017.5]	5630 [4290.0, 6732.5]	5655 [4492.5, 7405.0]	6060 [4530.0, 6647.5]	0.463*
Hb, g/dL	11.4 [10.8, 12.0]	11.5 [10.6, 11.9]	11.1 [10.5, 11.7]	11.5 [10.8, 11.9]	0.295*
Plt, 10^4/μL	19.5 [17.8, 21.3]	18.5 [17.2, 20.6]	19.0 [16.6, 22.3]	18.8 [16.6, 22,7]	0.514*
Alb, g/dL	3.5 [3.4, 3.6]	3.5 [3.4, 3.7]	3.5 [3.3, 3.7]	3.6 [3.4, 3.7]	0.247*
hsCRP, mg/L	0.78 [0.29, 2.21]	0.46 [0.25, 1.62]	0.82 [0.25, 2.15]	0.56 [0.25, 1.78]	0.142*
IL-6, pg/mL	7.2 [5.9, 21.3]	7.7 [4.7, 9.7]	8.3 [6.1, 13,1]	9.2 [4.6, 11.4]	0.814*
DW, kg	54.9 [47.0, 60.6]	54.9 [48.0, 60.4]	54.9 [48.4, 60.4]	54.4 [48.4, 60.6]	0.974*
β_2-MG, mg/L	25.1 [19.7, 27.6]			27.2 [21.8, 28.9]	< 0.05**
Corrected Ca, mg/dL	8.5 [8.3, 9.1]	8.4 [8.1, 8.9]	8.6 [8.2, 8.9]	8.5 [8.1, 8.8]	0.300*
IP, mg/dL	5.1 [4.7, 5.5]	4.8 [4.2, 5.2]	4.7 [3.9, 5.1]	4.5 [4.1, 5.1]	0.295*
Whole PTH, pg/mL	100.2 [73.6, 136.3]			83.5 [53.7, 154.7]	0.823**

Data are presented as median [IQR]. P values were calculated using the Friedman test (*) or Wilcoxon signed rank sum test (**)

Alb albumin, *β₂-MG* β_2-microglobrin, *corrected Ca* corrected calcium, *DW* dry weight, *Hb* hemoglobin, *hsCRP* high-sensitivity C-reactive protein, *IL-6* interleukin-6, *IP* inorganic phosphorus, *IQR* interquartile range, *Plt* platelets, *PMF-21A* Filtryzer® PMF™-A, *WBC* white blood cells, *Whole PTH* whole parathyroid horomone

Table 3 Comparison of removal rates for different solutes (n = 20)

	FIX-210E eco (n = 9)	PMF-21A	*p* value	FIX-210S eco (n = 11)	PMF-21A	*p* value
BUN	79.7 ± 5.3	80.2 ± 4.2	0.674	74.1 ± 3.3	74.9 ± 3.8	0.284
Cr	71.7 ± 4.5	72.2 ± 4.0	0.608	67.3 ± 3.9	68.9 ± 3.5	0.155
IP	64.0 ± 6.0	63.6 ± 7.2	0.864	64.1 ± 4.3	63.6 ± 5.0	0.728
B_2-MG	78.8 ± 5.5	73.7 ± 3.8	< 0.001	74.8 ± 4.8	67.6 ± 6.9	< 0.001
α_1-MG	22.6 ± 3.8	18.8 ± 5.2	< 0.05	33.2 ± 7.4	15.4 ± 4.0	< 0.001

Data (%) are presented as mean ± standard deviation. *P* values were calculated using paired *t*-test

α₁-MG α_1-microglobrin, *β₂-MG* β_2-microglobrin, *BUN* blood urea nitrogen, *Cr* creatinine, *IP* inorganic phosphorus, *PMF-21A* Filtryzer® PMF™-A

Table 4 Comparison of removal amounts for different solutes and albumin leakage (n = 20)

	FIX-210E eco (n = 9)	PMF-21A	*p* value	FIX-210S eco (n = 11)	PMF-21A	*p* value
BUN, mg	11,783.3 ± 1438.9	10,483.3 ± 2216.4	0.198	13,813.6 ± 2667.6	13,540.9 ± 2213.0	0.744
Cr, mg	1275.0 ± 404.4	1318.3 ± 370.0	0.482	1659.5 ± 464.9	1682.7 ± 317.2	0.733
IP, mg	623.3 ± 146.0	643.3 ± 205.1	0.593	867.3 ± 158.3	842.7 ± 146.8	0.584
β_2-MG, mg	190.9 ± 43.5	3.9 ± 1.7	< 0.001	198.6 ± 51.8	3.6 ± 1.6	< 0.001
α_1-MG, mg	75.8 ± 18.2	6.0 ± 13.3	< 0.001	154.4 ± 47.7	1.2 ± 3.9	< 0.001
Alb, g	2.3 ± 0.5	1.6 ± 0.6	< 0.01	5.7 ± 1.0	1.5 ± 0.4	< 0.001

Data (mg or g) are presented as mean ± standard deviation. *P* values were calculated using paired *t*-test

α₁-MG α_1-microglobrin, *Alb* albumin, *β₂-MG* β_2-microglobrin, *BUN* blood urea nitrogen, *Cr* creatinine, *IP* inorganic phosphorus, *PMF-21A* Filtryzer® PMF™-A

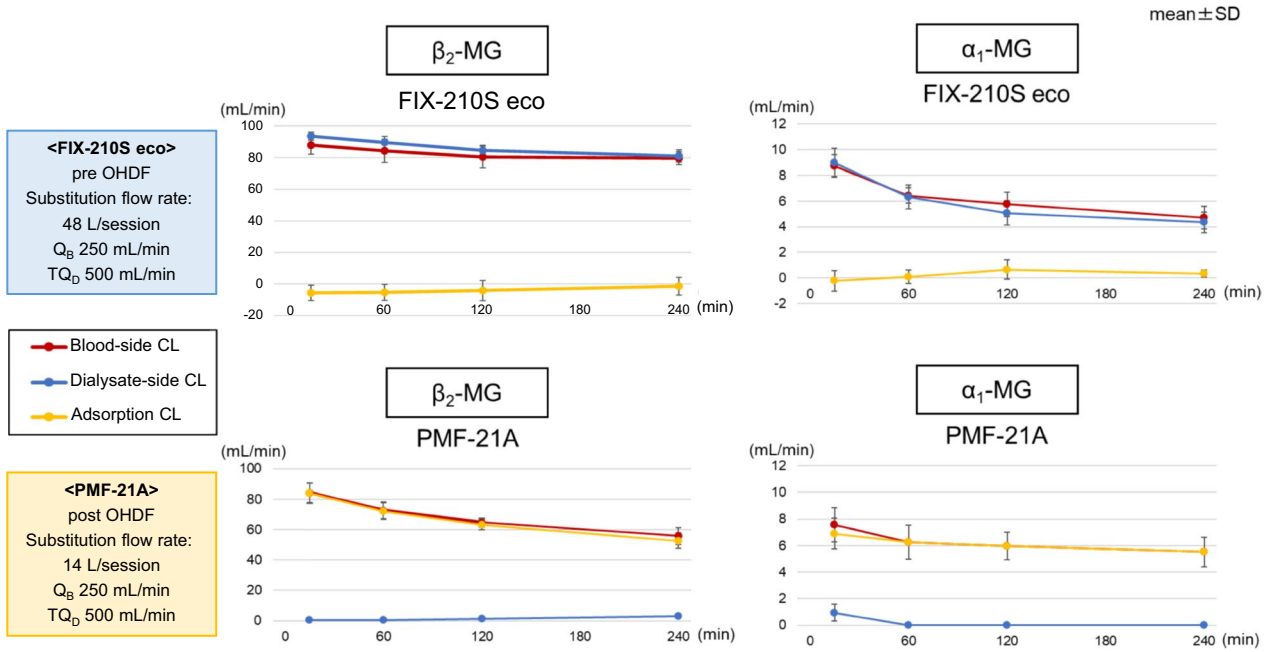

Fig. 6 Comparison of adsorption clearance (n = 6). *α1-MG* α1-microglobrin, *β2-MG* β2-microglobrin, *CL* clearance, *OHDF* online hemodiafiltration, *PMF-21A* Filtryzer® PMF™-A, *SD* standard deviation

mechanisms by which it improves pruritus. Fourth, although HAP involves a complex combination of multiple factors and requires cause-specific and comprehensive treatment strategies, the study could not examine the role of drug selection and skin care among those treatment strategies. Finally, it is desirable in the future to conduct a randomized controlled trial of long-term use of PMF-21A with monitoring of serum β_2-MG levels over time.

Conclusion

OHDF with PMF-21A may be more effective in improving HAP.

Abbreviations

α_1-MG	α_1-microglobrin
β_2-MG	β_2-microglobrin
Alb	Albumin level
ATA	Asymmetric triacetate
BPA	Bisphenol A
BUN	Blood urea nitrogen
Cr	Creatinine
GABA	Gamma-aminobutyric acid
HAP	Hemodialysis-associated pruritus
IL-6	Interleukin-6
IP	Inorganic phosphate
IQR	Interquartile range
OHDF	Online hemodiafiltration
PMMA	Polymethylmethacrylate
post-OHDF	Postdilution hemofiltration
pre-OHDF	Predilution hemofiltration
PTH	Parathyroid hormone
PVP	Polyvinylpyrrolidone
VAS	Visual analogue scale

Acknowledgements

The authors are grateful to all the medical staff who participated in this study.

Author contributions

NT conceived the study and wrote the first draft of this manuscript. JM, KU, and TY contributed to the study design, coordinated the study, and conducted the statistical analysis. JK, HK, ST, MM, and TM contributed to the study design and were involved in the production of the first draft of parts of this manuscript. The authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Review Committee of Tsuchiya General Hospital (Approval No. E220328-5) and was conducted in accordance with the principles of the Declaration of Helsinki. After obtaining prior verbal consent from each patient enrolled in the study, informed consent was documented in writing in their medical record.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 29 March 2023 Accepted: 1 August 2023
Published online: 04 August 2023

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