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CASE REPORT

Utility of Adding Once-Weekly Hemoadsorption to High-Volume Hemodiafiltration for Refractory Restless Legs Syndrome: A Clinical Case Report

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ABSTRACT

Dialysis improves survival in kidney failure but does not effectively remove larger uremic toxins, contributing to persistent symptoms like restless legs syndrome (RLS). High-volume hemodiafiltration (HDF) has improved these issues, but refractory cases may require combined therapies with hemoadsorption (HA). We present a patient with refractory RLS treated with HDF plus hemoadsorption using Jafron HA130 cartridges. The β2 microglobulin (β2M) reduction ratio was higher during HDF+HA (76.4% [75.8–77.8] vs. 72.9% [71.1–73.2]), with further improvement at $Q_B > 400$ ml/min (77.6% [77.2–79.4]). Despite similar baseline β2M levels, the patient's RLS score dropped from 32 to 0 points. Adding once-weekly hemoadsorption to high-volume HDF using HA130 adsorption may enhance refractory uremic symptom management, particularly at higher Q_B values. Given the scarce literature on this approach, our case highlights its potential benefits for dialysis patients with persistent uremic symptoms.

1 | Introduction

Dialysis increases the survival of patients with kidney failure; however, despite advances in the technique, there are still unmet clinical needs that impact the quality of life of this group of patients. High hospitalization rates and elevated mortality are not only due to the increasing age and comorbidities of the population but also to the intrinsic limitations of conventional hemodialysis (HD) due to the inability of this technique to eliminate the entire spectrum of uremic toxins [1].

The accumulation of larger molecular weight solutes can cause clinical problems such as dialysis-related amyloidosis, chronic kidney diseases (CKD) associated pruritus (CKD-aP), sleep disorders, and peripheral neuropathy [2]. Because of this correlation between the accumulation of larger toxins and persistent uremic manifestations, it is mandatory to continue looking for improved blood purification techniques in patients requiring renal replacement therapies. Among these new therapies is high-volume hemodiafiltration (HDF). The rationale for using HDF is based on simultaneous diffusive and convective transport, which combines the beneficial effects of conventional HD (mainly based on diffusive transport) with the advantages of large external convective volumes obtained with high-volume HDF, effectively eliminating small toxins by diffusion and larger solutes by convection [3]. Despite the proven benefits of high-volume HDF [4], there are still patients who may present persistent accumulation of medium-sized uremic toxins, like β 2 microglobulin (β2M) and residual uremic toxicity [5].

Among these clinical problems is restless legs syndrome (RLS), which is a sensory-motor disorder prevalent in HD patients that causes sleep interruptions, alters the quality of life, and has been linked to increased morbidity and mortality in maintenance

HD patients [6]. It is characterized by unpleasant sensations in the legs and a persistent impulse to move them. The disorder's pathogenesis is unclear, but factors related to the accumulation of uremic toxins, iron deficiency, anemia, genetic components, and lifestyle have been proposed as possible causes [7].

Improving clearance by adding a third solute removal mechanism, such as adsorption, should be considered for these patients. Hemoadsorption (HA) with HA130 cartridges has been described as effective in reducing medium toxin levels and uremic symptoms in hemodialysis patients, improving CKD-aP and RLS [8].

We present the case of a patient with refractory RLS and elevated β2M despite well-managed medical treatment, intradialytic exercise, and the application of high-volume HDF. Given the persistent symptoms, a combined approach was implemented by adding hemoadsorption with an HA130 adsorptive cartridge.

2 | Clinical Case

A 67-year-old woman with a history of arterial hypertension and stage G5 CKD secondary to granulomatous vasculitis with polyangiitis. She started on hemodialysis in 2007 and has remained on extracorporeal therapy ever since, always using a left radiocephalic arteriovenous fistula (AVF) as vascular access. In 2010, she was temporarily switched to automated peritoneal dialysis (APD) due to logistical reasons. Her prescription at that time included five nightly cycles, with 2200 mL per exchange, a dwell time of 1 h and 17 min, using 2.5% glucose-based solutions and calcium at 2.5 mEq/L. The last exchange was performed with 1400 mL of icodextrin at 9:00 a.m. Average ultrafiltration was clinically satisfactory. After 11 years of this treatment, she developed difficult-to-manage polyarthralgia, elevated β2M up to 46 mg/L, and poor volume management. For this reason, she was transferred to three-times-weekly high-volume HDF in 2021, with an effective blood flow rate (QB) > 400 mL/min, session length of 240 min, and achieving convective volumes consistently above 23 L per session. Despite the change in renal support therapy, she persisted with progressive worsening of diffuse chronic pain, β2M levels > 27 mg/L, and RLS. Symptoms of RLS had begun approximately 6 years after the onset of end-stage kidney disease and progressively worsened over time despite multiple interventions. Management included parenteral iron supplementation to target ferritin levels of 400–700 ng/mL and a TSAT of 20%–40%. Additionally, an intradialytic exercise program was initiated. Due to persistent RLS, she was referred to neurology for management optimization, receiving treatment with a buprenorphine patch, clonazepam, pramipexole, pregabalin, and sertraline without achieving reasonable symptom control.

Given the refractory nature and intensity of the RLS, which significantly interfered with her quality of life, hemoadsorption was added once weekly during the midweek HDF session for a total of four sessions over a 3-month period. She started HA with a Jafron HA130 cartridge (Jafron Biomedical Co. Ltd., Zhuhai City, China) added to her usual HDF prescription in the middle session of her three weekly therapies during the 240 min.

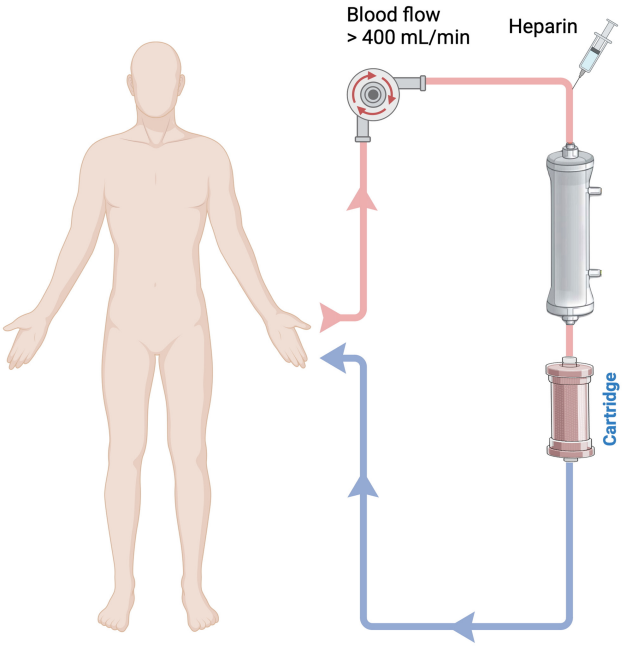

FIGURE 1 | HA130 cartridge installation after the filter in the hemodiafiltration circuit.

The cartridge was installed postfilter (Figure 1). β2M values were monitored pre- and posttherapy twice weekly (the first day of weekly HDF and then the day of HDF plus HA). According to the manufacturer's recommendation, Q_B was lowered to 250 mL/min on the day HA was applied in the first four sessions. Even with this Q_B, a convective volume of more than 23 L/session could be achieved during HDF with associated HA. Since there were no technical problems during the therapies in which adsorption was added, Q_B was subsequently raised to > 400 mL/min in all sessions (HDF and HDF plus HA). No technical problems were encountered with this Q_B during the HA application, and no significant alterations in the pressure profile of the circuit were observed. Restless Legs Syndrome Rating Scale (RLSRS) severity score validated for these cases was used (Table 1) [9].

Using data from the 25 sessions, a nonparametric analysis was performed using the Wilcoxon-Mann–Whitney test. Specifically, the analysis aimed to evaluate the impact of using the HA cartridge and whether a higher blood flow rate was utilized. The comparison was conducted between three groups: HDF alone (13 sessions), HDF + HA with a Q_B 250 mL/min (four sessions), and HDF + HA with Q_B > 400 mL/min (eight sessions).

A higher rate of β2M reduction was observed during HDF plus HA sessions with Q_B of 250 mL/min compared with HDF (76.4 [75.8–77.8] vs. 72.9 [71.1–73.2], $p = 0{,}038$), especially in those where a Q_B > 400 mL/min was used (77.6 [77.2–79.4] vs. 72.9 [71.1–73.2] $p = 0.001$). There was no difference regarding HDF plus HA with Q_B 250 mL/min and Q_B > 400 mL/min. The difference in the rates of β2M reduction of the different techniques is described in Figure 2. Although the rates of β2M reduction were higher when HA was applied, the baseline values of β2M before the following therapy remained unchanged (Figure 3).

TABLE 1 | Restless Legs Syndrome Rating Scale: RLSRS. Validated by the International Restless Legs Syndrome Study Group, the severity and frequency of symptoms in patients with restless legs syndrome are evaluated.

Question	Score
1. How would you rate the discomfort in your legs or arms from RLS?	0–4
2. How would you rate the need to move around because of RLS symptoms?	0–4
3. How much relief do you get from moving around because of RLS discomfort?	0–4
4. How severe is the sleep disruption from RLS symptoms?	0–4
5. How severe is the tiredness or sleepiness from RLS symptoms?	0–4
6. How severe do you consider your RLS to be overall?	0–4
7. How often do you have RLS symptoms?	0–4
8. On average, how severe are your RLS symptoms on a typical day?	0–4
9. How severe is the impact of RLS on your daily activities (family, work)?	0–4
10. How severe is the disturbance in your mood due to RLS symptoms?	0–4

Note: Ranking by total score: **None:** 0 point; **Mild:** 1–10 points; **Moderate:** 11–20 points; **Severe:** 21–30 points; **Very severe:** 31–40 points. The total score categorizes symptom severity into five levels: none, mild, moderate, severe, and very severe. The following rating scale is used for responses: None = 0; Mild = 1; Moderate = 2; Severe = 3; Very Severe = 4. RLS stands for Restless Legs Syndrome.

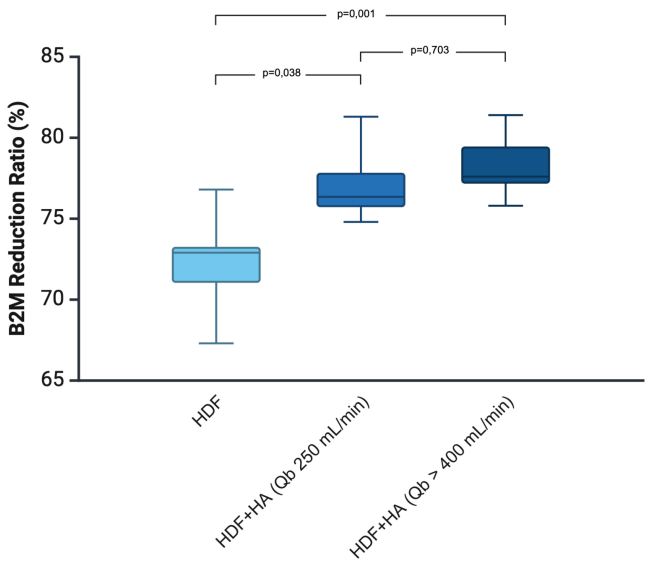

FIGURE 2 | Comparison of β2M RR across treatment modalities. A Kruskal–Wallis test was performed using data from all treatment sessions to compare the β2M RR across the three groups, revealing a significant difference ($p < 0{,}001$, not shown in the graphic). Post hoc analysis using the Dunn test with Bonferroni correction confirmed group differences. The higher differences in β2M RR were observed in the HDF + HA with Qb > 400 mL/min compared to HDF alone.

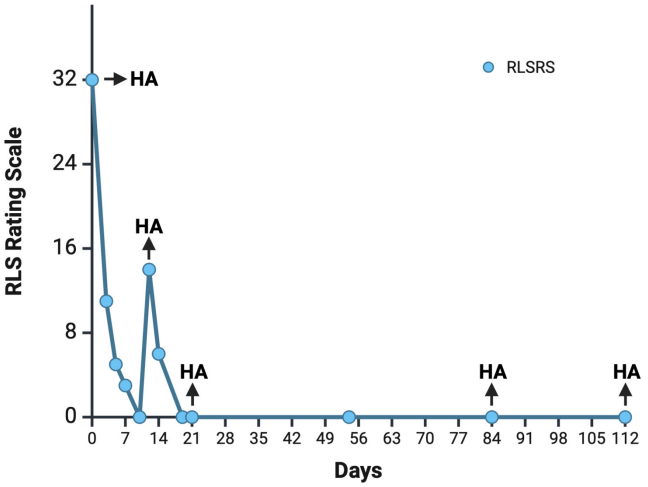

FIGURE 3 | Restless legs score during follow-up, with exercise and hemodiafiltration plus hemoadsorption. HA with arrows represents the HDF sessions with HA130.

Despite maintaining baseline (predialysis) β2M values similar to those before starting HA, a rapid improvement in symptoms was observed with the application of HA, which had not been observed with previous therapies. In addition, a drop in the restless legs score from 32 to 0 points was observed, maintained until the end of the 3-month follow-up (Figure 3).

3 | Discussion

The HA130 cartridge contains styrene-divinylbenzene copolymer beads that efficiently adsorb large middle molecules and various uremic toxins (both endogenous and exogenous, including protein-bound uremic toxins (PBUT), hydrophobic substances, cytokines, complements, free hemoglobin, and residual drugs) [10].

The use of HA with HA130 cartridges has shown benefits in reducing uremic symptoms in maintenance HD patients. Compared to HD alone, improved CKD-aP and decreased parathyroid hormone (PTH) and calcium-phosphorus products have been observed. Additionally, it has been observed that HA is superior to HD in eliminating medium and large uremic molecules, which translates into better quality of life and mortality [11]. On the other hand, the persistent inflammatory state of renal failure could be relevant for developing RLS in dialysis [12]. Thus, adding HA could contribute to reducing the microinflammatory environment of these patients [13].

Specifically, HA treatment is recommended once a week for patients who meet the criteria for the diagnosis of RLS (International Restless Legs Syndrome Study Group—IRLSSG) with an RLSRS severity score of > 11 points. Zhang et al. observed that after 3 months of treatment with HD plus HA130, the patients' severity scores decreased from 25.13 ± 6.24 to 7.56 ± 1.21, and the effective treatment rate was 97.78% [14], which was consistent with the results observed in our patient.

The β2M reduction rates were significantly higher when a higher Q_B was used than HDF without HA, and no technical

issues were observed (Figure 3). It is essential to maintain an optimal blood flow rate without altering the patient's usual prescription. Our group previously published a study demonstrating that using $Q_B > 350$ mL/min was safe, with no complications related to the therapy. Additionally, we observed an effective removal of PBUT at these higher flow rates without impairing the clearance of small and middle molecules, as blood flow was not reduced [15].

Regarding β2M removal, the reduction ratio measures only the relative reduction between the start and end of the session, failing to account for interdialytic fluctuation, where toxins can reaccumulate due to ongoing endogenous production and tissue redistribution. This suggests that, although RR provides immediate insights, it does not fully capture the progressive improvements or sustained clinical benefits, which require long-term monitoring.

To date, there are no data on the combination of high-volume HDF with HA for the management of residual uremic symptoms, so we consider that the report of this clinical case will be of great scientific value and could apply to other scenarios of complications associated with the accumulation of uremic toxins not removed by standard techniques.

4 | Conclusions

Adding once-weekly hemoadsorption to high-volume HDF using HA130 adsorption cartridges may improve refractory uremic symptoms such as RLS, especially when higher Q_B values are used. This combined treatment modality, poorly characterized in current literature, provides valuable insights and potential implications for future applications in managing chronic dialysis patients.

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Ethics Statement

All subjects enrolled in this research have given their informed consent, which has been approved by my institutional committee on human and research, and this protocol has been found acceptable by them. In 2023, the Scientific Ethics Committee of the Servicio de Salud Metropolitano Oriente reviewed and approved this case report. No decision reference number was informed.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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