

Review: the effect of polymethylmethacrylate dialysis membranes on uraemic pruritus

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The clinical burden of uraemic itching

Despite improvements in dialysis technology, including the development of novel biocompatible membranes and ultra-pure dialysate, uraemia-associated pruritus (UP) remains a common and significant public health issue [1]. Not only does this distressing symptom profoundly impact on the quality of life and sleep, but recent evidence shows that pruritus is also associated with poor patient outcome. In the international Dialysis Outcomes and Practice Patterns Study (DOPPS) [2], which evaluated more than 18 000 patients on haemodialysis (HD) therapy, pruritus was associated with a 17% greater mortality risk, an effect that was no longer significant after adjustment for measures of sleep quality. Nonetheless, nephrologists and other health care professionals often fail to recognize and adequately address the pruritus associated with chronic uraemia. The prevalence of chronic kidney disease (CKD)-associated pruritus varies substantially, ranging from 22 to 90% [2–6]. In the largest and most recent epidemiological study to date, the prevalence of CKD-associated pruritus was 42% [2]. Although this is a lower prevalence than initially reported, pruritus in patients with CKD remains frequent and continues to be a significant public health concern.

Role of the haemodialysis treatment

Pruritus was reported to increase just before HD treatment and to be relieved afterward [7], which is possibly explained by dialytic removal of causative molecules (possibly bile acids, urea and other uraemic toxins). Conversely, others have reported a greater intensity of itch during or after HD, possibly explained by hypersensitivity to components of the extracorporeal circuit such as blood tubing, dialysis catheters, cellophane adhesives and nickel-containing needle tips [8]. Acetate solutions, ethylene oxide

and aldehydic disinfectant have also been associated with pruritus in the HD setting [9,10].

Inadequate dialysis [6,8] is supposed to increase UP. A small pilot trial initially demonstrated that enhancing dialysis efficacy could control UP [11]. Moreover, the improvement of urea Kt/V from 1.05 to 1.24 by increasing the dialyser membrane area to more than 0.3 m² induced a reduction in renal itching score within 3 months [8].

The improvement in uraemic pruritus in HD patients increasing dialysis dose is supported by results from DOPPS I data, but not DOPPS II data in which this relationship was not significant ($P > 0.75$) [2]. This inconsistency in the association of Kt/V and pruritus raises concerns regarding the importance of this relationship. In fact, dialysis adequacy, assessed as Kt/V values, did not correlate with the frequency of UP in large epidemiological studies [2,12]. It must be acknowledged that Kt/V assesses dialysis efficacy by calculating the clearance of urea and does not take into account the removal of middle molecular weight (MW) toxins, which are implicated in the pathogenesis of UP [6]. Therefore, the possibility that Kt/V is not a reliable tool in this setting needs to be considered. In essence, although not supported by rigorous evidence-based findings, the optimization of dialysis efficacy remains one of the basic approaches in the treatment of UP [13]. On the other hand, the probability that proteins of middle MW, the HD clearance of which is indirectly monitored by means of β_2 -microglobulin levels, may be involved in the pathogenesis of uraemic neuropathy and, thus, the onset of UP could be of greater relevance. In fact, a relationship between circulating levels of β_2 -microglobulin (which often accumulates in end-stage renal disease patients) and UP has been shown [6].

Which kind of dialysis membrane for UP?

Nowadays, the suggestion that the reduction in UP is a result of the new, more biocompatible dialysers is still a matter of debate. The absence of significant differences in UP frequency or severity between HD and PD patients

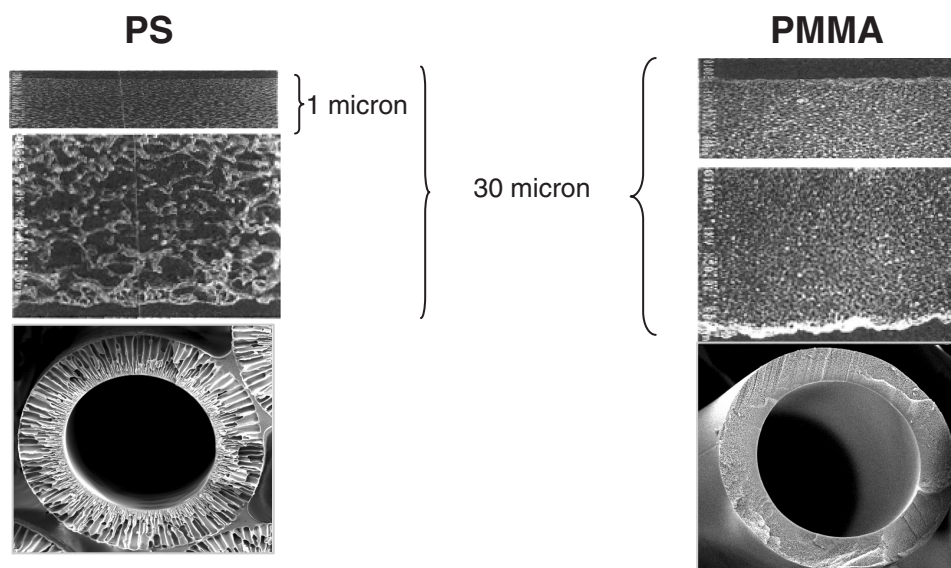


Fig. 1. Different ultrastructural features of polysulphone and polymethylmethacrylate-based membranes.

[7] has resulted in the role of blood-to-filter contact reaction as one of the potential causative factors of UP being questioned.

Szepietowski *et al.* [14] reported that patients dialysed using polysulphone membranes more commonly experienced pruritus than those using haemophane or cuprophane dialysis membranes. On the other hand, Kato and co-workers found that the severity of UP score was less in HD patients using polysulphone membrane compared with those using cellulose membrane despite a similar degree of dialysis efficacy [15]. High-flux polyacrylonitrile membrane was also noted to reduce UP in HD patients [16].

Although synthetic dialyser membranes seem to diminish UP, a more recent study found no correlation between pruritus intensity and type of dialysis membrane [6]. In addition, CKD-associated pruritus was reported to completely resolve after renal transplantation [17], although in common experience, some patients continue to experience pruritus post-transplantation.

Biophysical properties of the polymethylmethacrylate membrane

Polymethylmethacrylate (PMMA)-based dialysis membranes are synthetic membranes with good solute permeability and a high degree of biocompatibility, which is thought to be related to the hydrophobic nature of the polymer [18,19]. They are also unique insofar as they can remove proteins by adsorption as well as permeation. Uraemic blood contains a number of solutes that differ from those found in normal subjects and may relate to various morbid states, and it has recently been confirmed that PMMA membranes can also remove solutes of greater MW, such as the free immunoglobulin light chains that have an MW of 56 000 Da, which usually exist as dimers [20], and cannot be removed by membranes such as polysulphone membranes designed to function by permeation alone (Figure 1). Proteomic analyses of the serum, outflow

dialysate and adsorbed proteins on dialysis membranes during HD treatment have clearly shown that membrane adsorption is an important mechanism for the removal of middle MW proteins [21]. Obviously, peptide or protein adsorption onto a dialysis membrane may depend not only on the membrane material, but also on the peptide or protein, and it has been widely recognized that PMMA dialysers adsorb solutes such as cytokines and some cationic compounds. In this regard, PMMA may work as a sorbent, which could be useful for reducing the inflammatory burden of patients on maintenance HD. Among the various PMMA membranes, the BG-U series is characterized by a weak anionic charge and great adsorption capacity. These membranes were developed using a co-PMMA polymer to increase the removability of small molecules without affecting the removability of β_2 -microglobulin and are, therefore, more porous and have a more homogenous pore size.

Long-term clinical experiences with PMMA-based dialysis membranes have clearly shown a multifaceted clinical improvement for the HD patient [22].

Clinical experience with PMMA

The introduction of PMMA filters for HD resulted in itch reduction in four studies [23–26]. The rationale was that PMMA filters may improve UP by adsorption and permeation of ionic substances or cytokines. Hypothetically, uraemic blood contains a number of solutes that differ from those in healthy individuals. PMMA filters may remove solutes of greater MW by adsorption and permeation. Moreover, like other biocompatible dialysers, PMMA induces a less pronounced release of cytokines, which are believed to contribute to the development of UP.

In the study of Kato *et al.*, a prospective crossover trial in Japan [23], the authors clearly showed that the PMMA membrane effectively reduced UP in dialysis patients without any relationship with patient's age, dialysis duration or

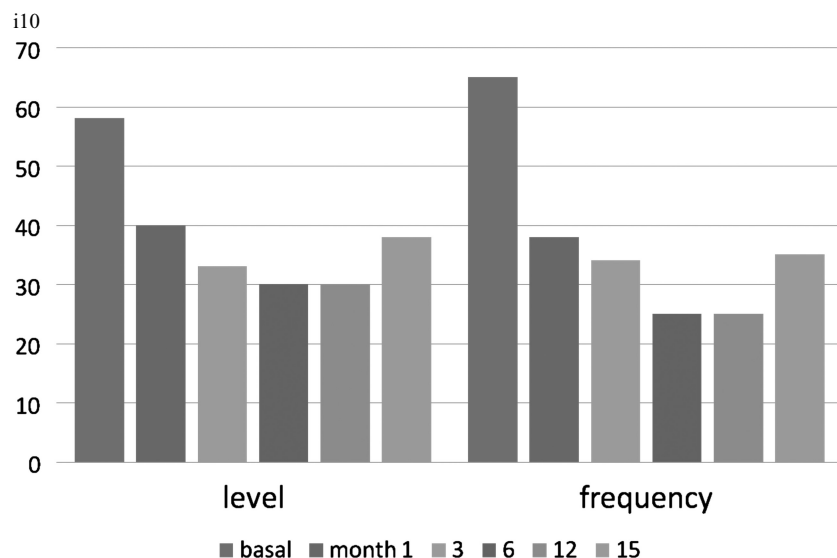


Fig. 2. Frequency and level of UP in HD patients: VAS scores in conventional (basal) versus PMMA membrane (12 months follow-up) and finally evaluation 3 months later (month 15, personal data).

efficacy, serum calcium, phosphorus and parathyroid hormone levels. They examined the TNF- α system but were not able to show any significant change. The UP scales remained lower during the additional 3 months despite the return to conventional membranes.

Lin *et al.* also showed a reduced burden of UP using PMMA dialyser membranes [24]. As in the previous study, the beneficial effects started after 1 week of PMMA use and lasted for 8 weeks after stopping that membrane. Also, in this study, there was no relationship with biochemical or immunological parameters, including cytokine activation.

In 69 HD patients with marked itching, the dialysis membrane was switched from other membranes to the BG series, which are weakly anionic PMMA membranes. The symptom of itching evaluated on the visual analogue scale (VAS) reportedly decreased significantly at 8 weeks after the membrane change [25].

Finally, an Italian observational study was recently performed [26] to evaluate the clinical efficacy of the BG-U series of PMMA membranes in decreasing uraemic itching. The self-assessed VAS itching-strength scores decreased by 15% after 1 month, 30% after 2 months and 55% after 6 months, and itching duration decreased by, respectively, 10, 22 and 44% at the same time. Two months after the return to baseline conditions, the scores slightly increased. There were no statistically significant differences in the pre-dialysis blood chemistry values at the four study time-points, but after 6 months of treatment with the PMMA membrane, there was a significant decrease in post-dialysis β_2 -microglobulin levels ($P < 0.03$) and a trend towards a decrease in C-reactive protein levels. There was no change in dialysis efficiency as assessed by means of eKt/V. Furthermore, four patients showed a trend towards a lower incidence of intradialytic hypotension. An ongoing extension of this study confirms these results (Figure 2).

It needs to be said that these studies had some limitations because they were not blinded, there was no control group and the populations enrolled were quite small. It

needs also to be underlined that all these studies agree, reporting the beneficial effects of PMMA dialysers on UP. But how could PMMA affect UP?

The studies by Kato [23] and Lin [24] both excluded a significant impact of PMMA on dialysis-induced cytokine production or release. However, PMMA membranes can remove a wide variety of solutes *via* not only permeation but adsorption as well [27], which may yield some effects to HD therapy. It is well known that, compared with polysulphone membranes, PMMA membranes remove a wider variety of solutes, greater amounts of solutes and adsorbed proteins over the entire range of MWs [25]. Their pore size distribution was designed to improve removal by adjusting adsorption and convection. The PMMA membrane adsorbs a wide variety of molecules. The rate of adsorption of β_2 -microglobulin is especially high. The removal of β_2 -microglobulin by adsorption is one of the typical characteristics of PMMA membranes. The weakly anionic PMMA membrane (BG series) has superior adsorption characteristics for basic proteins. As an example, PMMA membranes can remove free immunoglobulin light chains [25]. These chains have a MW of 28 000 Da and usually exist as dimers. Free immunoglobulin light chains cannot be removed by membranes designed for the removal of solutes by permeation, such as high-flux-type polysulphone membranes. Examining uraemic plasma using proteomic analysis, Aoike *et al.* [25] confirmed that slightly anionic PMMA membranes can adsorb components with a MW of up to 160 000 Da from the plasma of HD patients with pruritus.

Conclusions

Large solutes represent one of the last frontiers in the removal of possible uraemic toxins, and strategies for removing them include large pore membranes, adsorption materials and attempts to reduce their rate of formation pharmacologically or by means of dialysis. All of these

methods have advantages and limitations due to the intrinsic characteristics of the method, the nature of the solute and mainly their applicability in clinical practice. PMMA-based dialysis membranes provide a good opportunity to combine all three methods [18,28]. As BG-U (PMMA membrane) seems to be clearly capable of reducing uraemic itching, it can be speculated that ionic substances may be directly or indirectly adsorbed into their polymer composition. Although the adsorbability of PMMA membranes has some effects on the morbid states, further studies with proteomic analysis, epidemiological observations or development of new membranes aimed at those effects are needed.

Conflict of interest statement. None declared.

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