Review Article

Update on the Biocompatibility of Hemodialysis Membranes

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The blood of patients treated by dialysis is repeatedly exposed to foreign materials contained in the extracorporeal circuit, within which the membrane contained in the dialyzer is the largest element. Traditionally, the membrane was considered simply as a barrier between the blood and the dialysis fluid. However, the contact is also associated with the activation of coagulation, immune and cellular pathways, and the importance of repeated contact (often broadly referred to as "biocompatibility") has become an important clinical issue. Links between renal failure, dialysis and inflammation, and the role played by dialysis fluid has further focused on the membrane. The purpose of this paper is to review the recent developments in hemodialysis membranes, and to discuss their biocompatibility and role played in morbidity and mortality associated with dialysis treatment. [*Hong Kong J Nephrol* 2004;6(2):74–8]

Key words: hemodialysis, biocompatibility, membrane, endotoxin

對於長期接受血液透析的病人，其血液必需重複暴露於體外的環境中，其中透析裝置的人造半透膜元件為最主要的部分。半透膜不僅是血液與透析液間的一道屏障，更可能會激發一系列的生物效應，包括凝血與免疫系統的活化。事實上，半透膜與透析接受者的生物融和性 (biocompatibility)，是決定透析治療成功與否的主要因素之一，近年來亦已成為血液透析研究的重要課題。本文回顧了近年血液透析半透膜的發展狀況，並對其生物融和性與透析治療長期預後間的可能關係作出探討。

Introduction

The process of hemodialysis is essentially a procedure whereby molecular solutes, accumulated as a consequence of metabolism and dietary product breakdown, and fluid are removed from the blood across a semipermeable membrane contained in the artificial kidney or hemodialyzer. The hemodialyzer forms a part of the extracorporeal circuit and represents the major non-physiologic surface to which the blood is exposed.

Historically, membranes were considered passive permselective barriers. However, since the patient's blood is repeatedly exposed to such materials, the importance of such contact (often broadly referred to as "biocompatibility") has become an important clinical issue. The recognition of links between renal failure, dialysis and inflammation, and the role played by dialysis fluid has further focused on the membrane as a barrier to endotoxins and endotoxin fragments.

The purpose of this paper is to review the recent developments in hemodialysis membranes and discuss their biocompatibility and the role played in morbidity and mortality associated with dialysis treatment.

Materials and Structure of Dialysis Membranes

Although membranes may be manufactured from a variety of materials, those used historically for blood purification owe their origins to cellulose tubing used in food manufacture. Cellulose-based membranes remained the sole category of membrane until the 1970s, when the first synthetic membranes were introduced. The classical cellulose membranes were supplemented by modified cellulose membranes in the 1980s; today, a wide range of cellulosic and synthetic materials are

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available for use in renal replacement therapy. Industrial estimates indicate that in 1984, the worldwide use of unmodified cellulose, modified cellulose, and synthetic membranes was 75%, 15%, and 10%, respectively, which had changed to 10%, 39%, and 51% by 2001.

The clinician is faced with a bewildering choice of membranes (Table). Comparative classification of membranes is complex. Different comparison criteria such as membrane permeability, structure, and bioreactivity have all been used, but there is no internationally agreed classification. The classification in the Table compares membranes in terms of their chemical composition. The list is not exhaustive as new membranes are continuously being introduced.

The selection of a membrane is made on a number of different criteria, the most important being solute transport and hydraulic permeability characteristics and the treatment philosophy. For example, low-flux dialysis favoring the removal of low-molecular-weight solutes may be performed using membranes manufactured from cellulose, modified cellulose, or synthetic polymer blends. High-flux dialysis offering enhanced removal of small molecules and reduced treatment times (when used in combination with high blood and dialysate flow rates) can be performed with modified cellulose or synthetic membranes. Such treatment, however, remains inferior in its ability to remove larger molecular-weight solutes compared to hemodiafiltration or hemofiltration, which require the use of high-flux membranes. Such membranes are predominantly manufactured from synthetic materials. Other factors determined by local economic or environmental considerations can also play a role in the ultimate choice.

Biocompatibility of Hemodialysis Membranes

The definition of biocompatibility in the Dictionary of Biomaterials is "the ability of a material to perform with an appropriate response in a specific application". This definition is based on the principle that a biomaterial has to perform and not simply exist, that it has to be associated with appropriate responses to ensure satisfactory performance. It recognizes that the response to a material will vary from one situation to another, and that the appropriateness may vary. Furthermore, it allows a distinction to be made between biocompatibility and biologic safety. The main difficulty with this definition is that the applications of materials in the clinical setting are varied and there may be little commonality with the appropriateness of the responses. Williams, responsible for the original definition, has recently suggested that the biocompatibility of a medical device that is repeatedly in contact with blood may be considered as "the ability of the device to carry out its intended function within flowing blood, with minimal interaction between device and blood that adversely affects device performance, and without inducing uncontrolled activation of cellular or plasma protein cascades" [1]. Based on this definition, membranes with minimal activation of cellular or plasma protein cascades may be considered biocompatible.

Biologic Events at the Membrane Surface

The membrane in a dialyzer represents a large non-

Table. Hemodialysis membranes

Classical cellulose	Manufactured by a regeneration process	Cellulose Cuprophan®
Modified cellulose	Membranes in which the hydroxyl groups forming part of the cellulose molecule are substituted or modified during the manufacturing process	Hemophan™ Excerbane™ SMC™ Cellulose acetate Cellulose tri-acetate Cellulose di-acetate PEG modified cellulose
Synthetic	Naturally hydrophilic Hydrophilic through blending or manufacturing process	Ethylene vinyl alcohol Polysulfone* Polyethersulfone* Polyamide Polyacrylonitrile* Polymethylmethacrylate Polyarylethersulfone* Polyamix™

*Available from a range of manufacturers.

physiologic surface to which blood is exposed during each treatment. Such exposure results in the deposition of proteins onto the membrane surface, activation of the complement system, kinin, and coagulation and fibrinolytic pathways, as well as activation of the cellular elements of blood on each occasion (Figure 1). The magnitude of these events is governed by a variety of factors, including chemical composition and surface character, with synthetic materials outperforming materials based on cellulose in many indices [2,3]. The distinction between modified cellulose and synthetic materials, however, is less distinct. Both cellulose-based and synthetic membranes tend to be treated as generic groups. However, despite a similarity in the base material, membranes can behave in different ways when in contact with blood [4]. This is due partly to the material surface and partly to other factors related to the patient (anticoagulation, hemodynamic stability) or the treatment technique.

A clear understanding of the reasons for differences between membranes manufactured from similar blends of materials, e.g. polysulfone, is lacking. Recent studies suggest that the differences may be a result of variation in the degree of cross linkage between the polymers used [5].

The characterization of membranes in terms of biocompatibility can be made on the basis of a number of different parameters. Historically, complement activation (and the associated neutropenia due to the activation of complement receptors on the cells) was widely used for comparing membranes. Since many of the events associated with membrane blood contact have clinical sequelae, current emphasis focuses on the elucidation of the molecular mechanisms involved, for example, the release of oxygen radicals (oxidative stress) and intra-granular proteases secondary to neutrophil activation. This is of clinical interest since oxidative stress contributes to morbidity in hemodialysis patients, but the role of the membrane remains unclear [6,7]. Clearly, it would be of benefit to minimize generation of oxidative stress by the membrane. One approach has been to bond vitamin E to the membrane [8].

Membranes are permeable, and while the extracorporeal circuit is sterile, this is not the case for the dialysis fluid pathway. Patients undergoing regular dialysis treatment are subject to inflammation [9]. Although inflammation can arise from a variety of causes, the water used to prepare the dialysis fluid undergoes rigorous treatment to remove chemical contaminants. The absence of chlorine in the treated water permits the proliferation of bacteria in the distribution network unless there is rigorous attention to the sterilization and design of the water distribution network and dialysate pathways. Bacterial proliferation leads to the formation of biofilm which, once formed, is difficult to eradicate. Such films are dynamic and release bacteria and endotoxins with cytokine-inducing activity [10]. The membrane may act as a barrier to the transport of intact bacteria into the circulation, but lipopolysaccharide (LPS) fragments have the capacity to pass across the membrane. Both cellulose and synthetic membranes can adsorb LPS fragments, although the adsorption is minimal in the case of cellulose. Adsorption in synthetic membranes occurs in the outer layer of the membrane and is governed by the hydrophobicity of the membrane, the polymer composition, and the asymmetric structure of the membrane (Figure 2). It should be emphasized, however, that not all synthetic membranes have the same ability to retain endotoxins [11]. The potential of synthetic membranes to adsorb cytokine-inducing fragments has led to their use as dialysis fluid filters, adding extra protection for the patient (Figure 3). Utilization of such filters to improve the quality of dialysis fluid has resulted in improvement in patient nutritional status, inflammation, and response to erythropoietin [12–15].

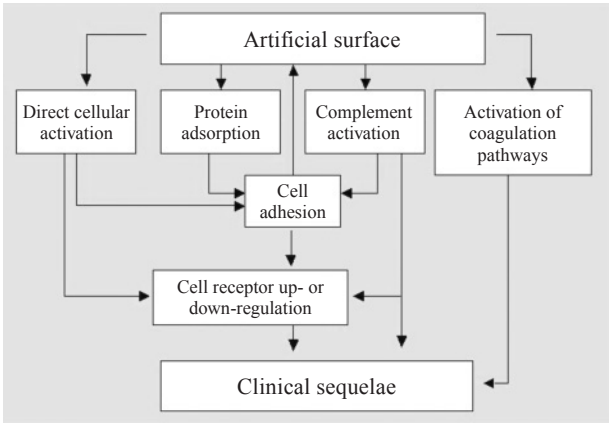

Figure 1. Blood pathway activation following material contact.

Does Biocompatibility Influence Patient Mortality and Morbidity?

Links between the development of clinical problems and the membrane type have been suggested in retrospective analyses [16]. Cardiac events are a major cause of death in dialyzed patients. This is due, at least in part, to the high prevalence of atherosclerotic coronary heart disease. To a large extent, coronary lesions are acquired in the predialytic phase of chronic renal failure, but factors related to the dialysis procedure itself may also influence early or late events in atherogenesis. The second most common cause of death in dialysis patients is infection. Activated proinflammatory pathways have the potential to produce a diminished immune response.

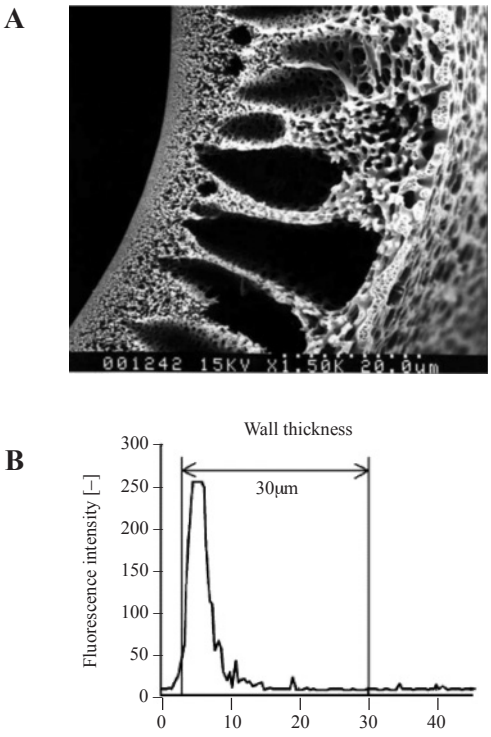

Figure 2. (A) Membrane structure of polymer blended membranes. Three distinct regions are visible: an inner selective layer with an approximate thickness of 0.1–0.5 mm, a support layer to stabilize the inner layer, and a finger-type support structure that gives the membrane additional mechanical stability. This layer has a thickness of 40–45 mm and presents an external skin with hydrophobic domains. These hydrophobic domains are critical in endotoxin entrapment from the dialysis fluid. (B) Visualization of endotoxin trapping in the wall of a synthetic membrane manufactured from a polyester-polymer alloy. The highest density is seen on the outer wall of the fiber, with no detectable endotoxin in the blood lumen. (Adapted from: Hayama M, et al. Visualization of distribution of endotoxin trapped in an endotoxin-blocking filtration membrane. *J Membr Sci* 2002;210:45–53. Reproduced with permission.)

Definitive evidence relating to the role of biocompatibility and outcomes is lacking, as the results of prospective randomized studies are conflicting. Furthermore, it has been difficult practically to separate the effects of biocompatibility and flux [17,18].

The recently completed HEMO study sought to address this complex issue [19]. However, the results indicated that death from any cause was not significantly influenced by either the dose of dialysis or the flux of the dialysis membranes used. The use of high-flux dialysis, however, was associated with reduced risks of specific cardiac-related events. The effect of high-flux dialysis on all-cause mortality seemed to vary, depending on the duration of prior dialysis, since patients entered the study after varying periods on dialysis. A European study (the Membrane Permeability Outcomes study) addresses this issue in that only patients new to dialysis have been included. The results from this study are expected in 2005.

The HEMO study also found that, in respect of infection, the likelihood of infection-related death did not differ between patients treated with high-flux or low-flux membranes.

It has been speculated that membrane biocompatibility may have a role in patient survival and recovery of renal function in acute renal failure. However, a recent meta-analysis by Subramanian et al showed that synthetic membranes appeared to confer a significant survival advantage over cellulose-based membranes (cumulative odds ratio, OR, for survival, 1.37; 95% confidence interval, CI, 1.02–1.83; $p = 0.03$) [20]. There was, however, no association between membrane type and recovery of renal function (cumulative OR, 1.23; 95% CI, 0.90–1.68; $p = 0.18$). As with chronic renal failure, outcomes are likely to be dictated by factors other than the membrane, such as comorbid conditions and the dose of dialysis [21].

Future Developments

Membranes have evolved into barriers with well-defined functionality and minimal bioreactivity. The adequacy of treatments is still largely assessed by the ability to remove low-molecular-weight non-protein-

Figure 3. The Hospal Diaclear filter forming part of the dialysate fluid pathway used in the maintenance of a high level of microbiologic purity in dialysis fluid.

bound solutes such as urea. Despite this, removal of some low-molecular-weight compounds such as phosphate remains inadequate [22]. Evidence is also accumulating that the inability to remove low-molecular-weight proteins and peptides results not only in complications arising from their elevated levels, but also from their chemical modification by advanced glycation endproducts (AGEs) or advanced lipoxidation endproducts, for example, the development of dialysis-related amyloidosis [23]. AGEs also play a role in the development of endothelial dysfunction and the development of atherosclerosis [24]. Adequate removal may require the use of alternate non-membrane-based approaches such as adsorptive techniques or the inhibition of AGE formation [25].

Conclusions

A wide range of membranes are available for use in the treatment of renal failure. The universal use of one brand of membrane in favor of another is impractical. The question of whether synthetic membranes should be used in preference to cellulose or modified cellulose membranes based on available evidence favors synthetic membranes, but such use may be at an additional cost, particularly if high-flux synthetic membranes are to be used [17].

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