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Review Article

HEMODIALYSIS MEMBRANES: PAST, PRESENT AND FUTURE TRENDS

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ABSTRACT

Renal failure is one of the major health problems faced by many people all over the world. These patients choose either transplantation procedure or undergo hemodialysis. Approximately 28% people suffer from renal failures worldwide, among which a quarter are very critical. Patients who opt for hemodialysis have to undergo it regularly. The membranes used in hemodialysis are very vital. The first ever polymer used asan artificial hemodialysis membrane was collodion, which is a derivative of cellulose- trinitrate. This was the leading element for further research and applications in this field. Later collodion was replaced by cellophane and cuprophane since they had better performance and mechanical stability than the collodion. The major disadvantage of this was their less hemocompatiblity as they were made from unmodified cellulose. Nowadays the modified cellulose membrane comes with high-flux modification and thus very effective in many therapy like the hemodiafiltration and the hemofiltration. The success of hemodialysis is highly dependent on the membrane used.

Key words: Renal failure; hemodialysis; collodion; cellophane; cuprophane; hemofiltration.

INTRODUCTION

Experimenting in dialysis started almost thousands years ago. But dialysis as we know it has its roots in the 20th century. Dr. Willem kolff, a young Dutch physician is considered to be the father of dialysis. He constructed the first dialyzer in 1943. There had been a remarkable development in the treatment and therapies in the related field since then. There is also a tremendous impact in the research area regarding the renal failure and its cure. This is a medical condition where in the filtration of blood in body doesn't take place properly leading to accumulation of toxic waste materials. The main reason for this disease is sudden interruption in blood supply to kidney, accidents, injuries, complication in surgeries etc. These patients can either go for organ transplantation or hemodialysis. In hemodialysis the membrane used determines the success of the dialysis procedure. Membranes are of different pore size, those membranes with small size pores are called "low-flux" and those with higher pore size are called "high-flux". The initially used unmodified cellulosic membranes were highly permeable polyacrylonitryle and polysulfone membranes. Later on they were replaced by modified cellulosic membranes which had a very crucial stage of development[1]. Then on there had been a terrific increase in the use of modified cellulosic membrane in high efficiency and high flux segments. The main characteristics of modified cellulosic membrane include low wall thickness value, (6-15µm) and symmetric structure. Along with this the synthetic membranes were also emerging. Synthetic membranes are made of polymers and may have at least wall thickness value of 20µm[2]. They can be either structurally symmetric or asymmetric. During the last few decades researchers have been focusing on the biocompatibility of artificial membranes and the optimization of removal of uremic toxins by the membranes, because long term treatment may lead to complications such as amyloidosis heart, bone lesion etc[3]. The high-flux dialytic membrane is most recommended in the present days, since it is more biocompatible.

Types of Membranes Used

Unmodified cellulose membranes

The cellulosic membrane has a constituent component cellobiose, a saccharide[4].The most important characteristics of cellobiose is the high density of its hydroxyl groups, when considering the blood interaction with cellulose membrane. Although when blood gets in contact with any artificial surfaces it brings out the activation of an alternate complement pathway, but in case of unmodified cellulosic membranes the abundance of hydroxyl group makes this event clear. The characteristics of unmodified cellulosic membranes was considered clinically undesirable when reported at first but the demand for it declined over the years with the progress in other materials in the same area. The initial long term acceptance of cellulosic membranes was due to their high suitability for diffusion based hemodialysis. The hydrogel structures of the membrane allowed for the combination of low wall thickness and high porosity to be attained[5]. This characteristic allows high transport rate within the diffusive membrane, efficient removal of small uremic solutes like the urea and ceratinine. One more important characteristic of this unmodified cellulosic membrane is that they are symmetric with respect to their composition, thus providing a uniform resistance to mass transfer over the entire membrane wall thickness. Unmodified cellulosic membranes are also characterized by low mean pore size and hydrophilicity.

Modified cellulosic membranes

Modified cellulosic membranes were first used in 1980's. Modified cellulosic membranes are characterized by low wall thickness (6-15µm) and have symmetric structure. These also have larger mean pore size (22µm) than unmodified cellulosic membranes. This property of larger pore size of modified cellulosic membranes resulted in higher water permeability and middle molecule clearance. The two most commonly used dialyzers contain membranes where in the hydroxyl replacement mechanisms are much different. For cellulose acetate membranes, acetate group replaces almost 75 % of the hydroxyl group present on the cellulose

backbone. Compared to a hydroxyl group, an acetate group does not bind overzealously to a C3 molecule for the initiation of complement cascade[6]. Thereupon complement activation is attenuated, as is the leukopenic response, where in the WBC count decreases from baseline usually in 30-40% range. As production of cellulose triacetate membrane involves complete hydroxyl substitution replacement, further attenuation of complement activation and leukopenia is achieved[7]. Hemophane dialyzers are products containing modified cellulosic membranes. In case of hemophane only a mere 5% of hydroxyl groups are replaced. In this tertiary amine replacement is bulky shielding a greater a higher percentage of hydroxyl groups by steric method. The attenuation condition obtained in here is similar to the cellulose acetate dialyzer. The similar approach provides a low degree of hydroxyl substitution for synthetically modified cellulose (SMC), a recently developed membrane for which the substitution group is benzyl moiety.

Synthetic membranes

The need for developing synthetic membranes was due to the less solute removing ability and the complement path activation of the unmodified cellulosic membranes. Rhône-Poulenc developed the first synthetic membrane for dialysis in 1969[8]. Since then many a number of membranes have been developed including polysulfone, PMMA, polyamide etc. The large mean pore size and thick cell wall structures of the membrane allows high ultrafiltration at relatively low transmembrane pressure in hemofiltration. The main difference between cellulosic membranes and synthetic membranes are its chemical composition. Synthetic membranes are manufactured polymers called the thermoplastics. The synthetic membranes have a minimum wall thickness of 20 μm and can be structurally symmetric or asymmetric. Most of the polymers used nowadays are hydrophobic and need adding of hydrophilic agents to avoid too much protein adsorption on blood contact.

Biocompatibility of Hemodialysis Membranes

Biocompatibility generally refers to the ability of a material to perform with an appropriate host response in a specific situation[9]. The main use of hemodialysis membrane is to provide a semipermeable barrier for the transport of water and other solutes from blood compartment to the dialysate compartment. Interactions may occur between blood and the membranes as the membranes are not inert, subsequently leading to alterations in blood elements. Biocompatibility of hemodialysis membranes are mainly concerned with these interactions.

Defining biocompatibility of hemodialysis membrane

The scope of the subject and the definition of biocompatibility may often vary with development in the subject. But most of the researchers like to define biocompatibility as 'beneficial'. Considering an example, the adsorption of albumin to the membrane surface decreases the adhesion of platelets and adsorption of β2-microglobulin (β2MG) may decrease the plasma concentration of amyloidogenic substance[10]. This phenomenon may be hence considered as biocompatible by some. An alternative definition of biocompatibility is absence of agitation in blood elements. In another words there must be no adsorption or transformation of protein or nonproteinaceous substances, minimal mechanical shear at blood-membrane interphase and no spallation of substances into blood stream[11].

Complement activation of hemodialysis membrane

The interest in complement activation of hemodialysis membrane started initially from the observation of leukopenia (dialysis-induced). It was craddock and his team who first credibly demonstrated the complement activation of hemodialysis membrane using cellulosic membranes. The production of C3a and C5a products of complement activation was also later validated using cuprophane dialysis (Figure 1)[12]. The C3a have been widely used as the index of membrane biocompatibility. Through hemodialysis using cuprophane membrane, a 15-30 fold increase in dialyzer venous plasma C3a antigen concentration can be detected. Hemodialysis with cuprophane induced lower plasma C3a antigen levels than cellulose acetate membrane[13]. Because complement activation is temperature and divalent cation reliant, dialysis using cool dialysate or citrate anticoagulation also induces less complement activation[14,15].

Figure 1: The complement system of plasma proteins is an important part of the immune system that forms a cascade of factors that lyses foreign cells. The alternative pathway starts with the conversion of C3 into an active protease. C3 convertase splits C3 to form C3b and go on to form C5 activating convertase. Alternative pathway proceeds recruiting complement products like C6, C7, C8 and C9. Thus forming the membrane attack complex (MAC) and causing lysis of the related cell.

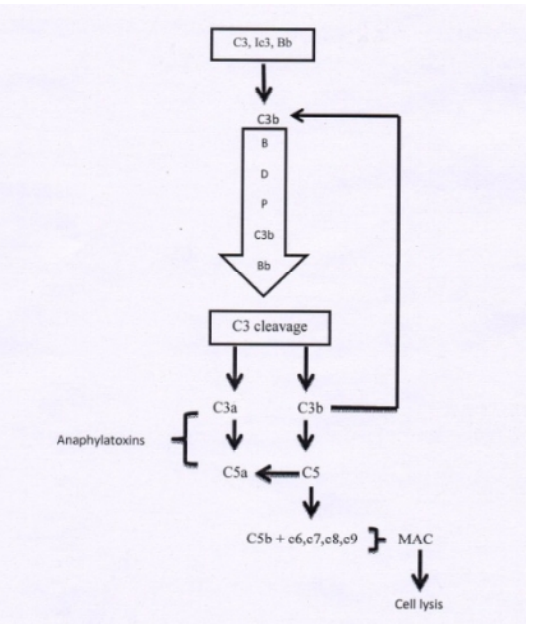

Figure 1: The alternate pathway cycle

Activation of terminal pathway of complement during hemodialysis

Activation of the alternative pathway of complement can at times result in the activation of the terminal components. This leads to the assemblage of the membrane attack complex (MAC)[16]. Recent studies have also shown the presence of these complexes in the plasma during hemodialysis. With enough concentration of these membrane attack complexes, these can stimulate arachidonic acid metabolism and induce cellulolytic conditions[17]. It is not likely that complement mediated lysis of erythrocytes May occurs to any significant level during hemodialysis. Sub lytic concentrations of membrane attack complexes can increase the delicateness of

erythrocytes leading to the decreased half-life of dialysis patient.

Indices of complement activation allied with hemodialysis membranes

Membrane attack complex (MAC) is also an index of complement activation of hemodialysis along with the C3a and C5a indices. Because these shows the complement activation of hemodialysis membrane at different levels with different action potentials. Here measure of one index does not substitute for the measurement of other, as C3 doesn't lead to equal molar activation of C5 or that of the terminal section. Recent studies show some interest in measurement of other C3 activation products as indices of C3 activation. Detection of some of them as iC3b and C3d.they may possess their own biological activities[18]. These fragments like iC3b and C3d may degrade further according to the environment they are present. Quantitation of particular fragment may not correctly give the total number of C3 molecules that have been activated. Cross reaction between present antibodies and C3 fragments can complicate the interpretation of assay.

Adsorption of dialysis membrane as index of biocompatibility

It has already been mentioned that adsorption of albumin to the dialysis membrane surface decrease the platelet adhesion and that adsorption of β2-microglobulin decreases the plasma concentration of the peptide. Both of these cases characterize a bioincompatible situation when considering the inert surface definition of biocompatibility, but beneficial otherwise. Adsorption of proteins is never beneficial; taking an example adsorption of fibrinogen to artificial surfaces promotes platelet adhesion and coagulation[11]. Another example for adsorption of beneficial substances dialysis membrane is AN69 membrane adsorbs more erythropoietin in vitro than cuprophane membranes do. Clinical impact of this still being undetermined, removal of erythropoietin is unbeneficial.

Upcoming Trends of Hemodialysis Membranes

Hemodialytic treatment of patients with either acute or chronic renal failure has had a dramatic impact on the mortality rates of these patients. But membrane based therapy is still incomplete, as rate of mortality and ill health of patients remain excessively high. So improvement in biocompatibility and perm selectivity of the hemodialysis membrane must be made. The extension of membrane technology to bio-hybrid devices utilizing stem cells will be another applicable advance for renal replacement therapy. The property of active reabsorptive transport and metabolic activity will add further benefit to the therapy of patients suffering from renal failure[19].

Traditional membranes

The concept of dialysis was first described by graham, utilizing a semi-permeable membrane and concentration gradient across membrane for easy transport of substances[20]. Cellulose-based materials are used for this purpose since the first human hemodialysis treatment with collodion membranes. Later, the rotating drum dialyzer created by Kolff and Berk and became the first appropriate device for widespread clinical use. The hollow-fiber dialyzers were used in 1960's, which had regenerated membranes as their principal membrane[21]. Concerns of biocompatibility came from the hydroxyl group of cellulose membranes led to the formation of a new membrane called the modified cellulose membrane. These modified cellulose membrane had more biocompatibility as the hydroxyl groups present in them were camouflaged by replacing with other chemical membrane materials. The vitamin E bonded membranes were developed in recent years, which had better biocompatibility and low hemodialysis related oxidant stress. Further synthetic membranes with larger pore sizes and high water permeability compared to cellulosic membranes were developed. These so-called 'high flux' membranes are prepared with hydrophobic base materials.

Living membranes

As the development is taking place in the hemodiafiltration with wearable and implantable devices the major drawback of the current membrane system is the reduction of filtration rate owing to protein deposition on membrane and thrombogenic obstruction of hollow fiber. This reduces the durability of filtration membrane. Micro fabricated capillary networks with microelectromechanical system techniques have also made practical developments lately[22]. The present system of membrane therapy focuses only on solute and removal in patients with either acute or chronic renal failure. The extension of the lost recovery, metabolic, and endocrine functions of the kidney depends on the development of living cells incorporated with renal tubule cells. The high-flux hemofiltration membrane and related extra-cellular matrix molecule layer thus act as support and immune barrier for the cells of the bioartificial tubule. The main aim of this is to replace the kidney metabolic activity to improve biologic homeostasis, including immunologic, cardiovascular, and mineral metabolism. A renal tubule cell may help in reabsorb a convectively produced ultrafiltrate. The resorption process is important to maintain volume homeostasis in a patient of ESRD demanding 5-10 ml/min of clearance function.

CONCLUSION

The membranes first used for a successful was collodion membrane, since then many a new membranes were developed with more biocompatibility and less blood membrane interactions. The initial trend of the membrane used for hemodialysis was cellulosic membranes, which later was replaced by modified cellulosic membranes and further by the synthetic membranes. The membrane therapy had several limitations that lead the researchers to look on for more developed membrane systems like the membranes with leverage materials and implanted devices. There may be many alterations to the blood elements when they come in contact with the hemodialysis membrane. These reactions can produce clinical image that may be acute or drastic as shown by anaphylactoid reactions. The exact clinical influences of each of these biocompatible events are difficult to determine for several reasons. It should be repeated that biocompatibility and beneficial effects of dialysis membranes differ depending upon the standards employed. The future improvements of hemodialysis membrane will mostly be leverage materials and microfluidics and nanofabrication technologies. The expansion of biohybrid devices utilizing hemodiafiltration membranes and stem cell bases will also advance present biocompatibility boundaries while providing more complete renal function replacement. The research and development to improve the quality of life of patients will go on improving day by day, which may be a boon for patients who currently receive relatively incomplete and nonphysiologic renal substitution therapy.

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