Biocompatibility of Dialysis Membranes

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Recent advances in medicine have been largely due to the exploitation of technological advances and innovations. Many of these innovations have required more invasive techniques and maneuvers that bring the human body in intimate contact with intrinsically foreign substances. New measurement techniques using plastic catheters, cardiac and joint prostheses, heart-lung bypass equipment and pacemakers are examples that come readily to mind; but perhaps nowhere is this exposure to foreign material more life saving than in hemodialysis where the process of removal of uremic toxins occur on a chronic basis, three times a week for many years.

The term biocompatibility refers to local or systemic effects that biomaterials may exert upon their contact with tissue. In the case of hemodialysis blood comes into contact with several types of foreign surfaces which range from the metallic surface of the needle that is inserted into the graft to the plastic in the blood tubing as well as different dialysis membranes. The subject of the talk, necessarily limited in scope will deal with the issue of biocompatibility of dialysis membranes.

In the large majority of cases, these interactions between the blood and biomaterials is clearly not lethal. However, before inferring this means that dialysis is completely biocompatible, we should remember that the large majority of patients do not feel well after dialysis and that the mortality rate of dialysis patients is still 10-15% per year. The extent to which biocompatibility of dialysis membranes is important in this morbidity and mortality is conjectural at present and more studies are needed to assess the contribution of blood-dialysis membranes interaction to these events.

Until recently, the only commercially available dialysis membranes in the United States were manufactured from a cellulosic material, either as cellophane or cuprophane. More recently, a number of other types of dialysis membrane material have been tested and introduced in the U. S. A., including cellulose acetate, polyacrylonitrile membrane, and the TORAY Industries PMMA membrane which exhibits excellent small and middle molecule clearance.

Our own interest in biocompatibility of dialysis membranes resulted from our experience at The Kidney Center in Boston where 350 patients are dialyzed every week. A few patients were initiated on the TORAY PMMA membrane artificial dialyzer (B-2-M) on an experimental basis to test the clearance of the membrane. At the end of the testing, the patients spontaneously requested continuation of their dialysis on the PMMA membrane because "they felt better". Based on these comments we initiated a small study to investigate the biocompatibility of different dialysis membranes.

Our study was undertaken to examine the effect of the cellulosic and noncellulosic membranes on the dialysis associated hypoxemia and neutropenia as examples of known biotoxicity, in an effort to clarify the mechanisms of these two phenomena and their possible interrelationship. Since the sterilization methods of dialyzers used in previous studies have not been specified and because there exists the possibility of a specific interaction between sterilization method (specifically dilute formalin solution) and the dialysis membranes, the effect of the sterilization method on each membrane was also studied.

Eight long term chronic hemodialysis patients undergoing three times weekly, maintenance hemodialysis were chosen for this study. None of the patients were known to have had recent or recurrent symptoms of fluid overload or cardio-respiratory diseases. Each patient was dialyzed with three different first use dialyzers namely the Cordis Dow 1.3 meters square using cellophane fibers, the Hospal RP6 using PAN flat sheet membrane and the TORAY Industries B2M manufactured with PMMA hollow fibers. Each patient was dialyzed twice with each
type of dialyzer, in one instance the dialyzer was dry sterilized (gamma rays for TORAY and ethylene oxide for the PAN and cellulotic membrane for Cordis-Dow and RP6) and in the other it was sterilized with formalin blood sterilization.

In this first study, we looked at the changes that occur in white blood cell numbers and blood gases drawn from the arterial line at various time intervals of dialysis, comparing it to the values pre-dialysis.

As far as the sterilization method, there was no statistically significant difference between formalin sterilized and dry sterilized membranes in any parameters tested for either the PMMA or cellulotic dialyzers. There was a trend toward greater hypoxemia with the formalin pre-treated PAN membrane and with the dry sterilized cellulotic membrane but this was not statistically significant. Subsequent results will thus be discussed with the data for each dialyzer representing aggregate data for the wet and dry sterilized membrane.

The relative change in white blood cell count was found to depend strongly on the type of membrane and was more pronounced with the cellulotic membrane than with either of the non-cellulotic membrane. The average white blood cell of patients dialyzed with the cellulotic membrane decreased to 34% of the pre-dialysis value at 15 minutes while it fell to only 86% of the initial value with the PAN and PMMA membrane.

When one looks at the changes in the neutrophil and lymphocytes separately, we again note that the cellulotic membrane induces a significant neutropenia with the neutrophil count decreasing to 20% of the pre-dialysis value at 15 minutes. The neutrophil count increased thereafter and following the first hour of dialysis exceeded pre-dialysis value such that at 180 minutes it was 140% of the pre-dialysis value. In sharp contrast to this, the percent change in the neutrophil count was considerably less with both non-cellulotic membranes with the minimum level to which neutrophils fell approximately 83% of the pre-dialysis value. There was no “over-shoot” observed with either of these two non-cellulotic dialyzers.

While there was no statistically significant differences in the percentage change of neutrophils between the PAN and PMMA dialyzers, there was a significant difference between the cellulotic and non-cellulotic membrane dialyzers at 7, 15, and 30 minutes, and later at 120 and 180 minutes. Of interest is that the lymphocytes count also showed a similar pattern of change in the function of different dialysis membranes at different times.

The maximum decrease in PO2 with dialysis for the three types of membranes were found to correlate with the extent of leukopenia. Thus, There was significantly more hypoxemia associated with the use of cellulotic membranes at 15 minutes, 30 minutes and at 60 minutes than with the PMMA or PAN membrane. Of interest is that there was no other statistical difference in the other parameters of the blood gas such as pH, bicarbonate and CO2.

These differences in biocompatibility between different dialysis membranes may have important clinical and therapeutic consequences in the dialysis treatment. Dialysis related hypoxemia induces a more profound hypotension during dialysis because there is no significant increase in heart rate or cardiac contractility that accompanies the hypotension. Combined with the enhanced affinity of the hemoglobin for oxygen, this may substantially decrease oxygen delivery to tissues particularly in patients with compromised cardiopulmonary status leading to a high incidence of cardiovascular morbid events during dialysis, particularly in older patients with lung disease and coronary atherosclerosis.

Dialysis induced leukopenia is also associated with functional and structural changes of the neutrophils and lymphocytes. Experiments on the chemotactic, adherence, and phagocytic ability of the white blood cells during dialysis has been shown to be significantly impaired during the time at which there is severe neutropenia and perhaps more significantly also at the time where there is rebound leukocytosis. The significant variation of the number and function of neutrophils with each dialysis may well contribute to the high rate of infection in dialysis patients.

The pathway of complement activation during dialysis has been shown by Craddock to be due to the activation of the alternative pathway which is an older system and responds to more basic stimuli such as activation by fungal and bacterial polysaccharides. Thus, it is not surprising that the polysaccharide structure of
Cellophane and cuprophane have been shown to be potent activators of the alternative complement system. Again, our results have shown that the extent of complement activation as measured by the total hemolytic complement assay, which is an aggregate measure of the activation of the complement system, correlates with the extent of neutropenia and is membrane dependent. Cellulosic type membranes activate the complement system to a much higher degree than the PMMA TORAY membrane dialyzer.

Another aspect of the blood-materials interaction across dialysis membranes is the activation of the intrinsic blood coagulation system, that is only aborted by the use of large doses of heparin. A number of studies indicate that fibrinogen is a major component of the absorbed protein level that forms on initial exposure of blood to bio-materials. Some of this fibrinogen appears to be replaced on the bio-materials surface fairly quickly by high molecular weight kininogen. This latter substance is necessary for the attachment and activation of Factor XIII and is activated by contact with negatively charged surfaces. Studies on patients who lack Factor XII showed that they do not have activation of the coagulation pathway when their blood is in contact with foreign substances in in-vitro systems. Once Factor XII is activated, the intrinsic blood coagulation system will proceed sequentially to produce fibrin.

There is suggestive evidence in the literature that pathways other than the complement cascade are activated when blood is in contact with dialysis membranes. This is also supported by our preliminary work on the activation of the brady-kinin system. For example, blood obtained from patients deficient in Factor XII (Hageman’s factor) results in markedly less leukocyte deposits on cellophane dialysis membranes. Although it is difficult to measure accurately Hageman’s factor, it is possible to measure one of the substrates on which active Hageman’s factor acts namely Kallikrein which has been shown to have neutrophil chemotactic ability and which in turns acts on another plasma protein substrate, kininogen to release the biologically active nonopeptide bradykinin. Bradykinin is a potent hypotensive agent, eliciting both increased capillary permeability and arteriolar vasal dilation. However, there has been no study which investigated the activation of plasma kallikrein and the release of bradykinin with different dialysis membranes. In summary, the possible inter-relationship between the Hageman’s factor pathways and the complement system as well as the coagulation pathway is being investigated at present, with the view that these pathways are part of the general blood materials interaction that occurs across dialysis membranes. In turn, these interactions appear to have significant clinical sequelae in chronic dialysis patients.