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Blood Compatibility in Various Hemodialysis Membrane Materials: A Review

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Abstract

In hemodialysis therapy, the contact between blood and the dialysis membrane causes biological reactions such as complement activations, the activation of blood cells and the coagulation system. Since 1960s, research has been conducted to develop dialysis membranes with excellent blood compatibility that prevents such reactions from occurring. The first dialysis membrane developed was a regenerated cellulose (RC) membrane. However, since transient leukopenia was observed when RC membranes were used, cellulose acetate (CA) membranes, in which one, two and/or all three hydroxyl groups of the RC is/are masked by corresponding numbers of acetyl groups, are currently being used. Conventional CA membranes have a homogeneous structure; however, asymmetric cellulose triacetate membrane (CTA) with a dense inner surface of hollow fibers has also been developed recently, which made it possible to have smoother surface of the membrane. This may make it harder for proteins and platelets to adhere to the membrane. In addition to cellulosic membranes, synthetic polymeric membranes such as polyacrylonitrile (PAN), poly(methyl)methacrylate (PMMA), ethylene vinyl alcohol copolymer (EVAL), polysulfone (PSf), polyethersulfone (PES), and polyester polymer alloys (PEPA) have also been developed. Since AN69®, one type of PAN membranes, has a strong electric negativity, it can adsorb and remove positively charged cytokines and complements. PMMA is well known to have adsorptive characteristic to β2-microglobulin and inflammatory cytokines. Recently, PMMA with weakened negative charge has been developed to inhibit platelet adhesion. PSf membranes have high solute and water permeabilities. In order to improve blood compatibility, PSf membranes coated with vitamin E or those with novel hydrophilic polymers have been developed. When selecting a membrane for treatment, much attention should be paid not only for solute and water permeabilities, but also for its blood compatibility.

Introduction

In hemodialysis therapy for end-stage kidney disease (ESKD) patients, blood and dialysate are brought into contact through the dialysis membrane to remove waste products and excess water. When blood contacts the dialysis membrane, blood cells, coagulation system, fibrinolysis system, kallikrein system, and complement system are activated. Therefore, dialysis membranes with excellent blood compatibility must be chosen to avoid such reactions to occur. In this article, we review blood compatibilities of each dialysis membrane material.

Dialysis Membranes

Dialysis membranes can be broadly classified into cellulosic membranes and synthetic polymeric membranes, among which the latter includes polyacrylonitrile (PAN), poly(methyl)methacrylate (PMMA), ethylene vinyl alcohol copolymer (EVAL), polysulfone (PSf), polyethersulfone (PES) and polyester polymer alloy (PEPA).

Cellulosic Membranes

The earliest mass-produced membrane material was made of a regenerated cellulose (RC) developed in the 1960s; however, the RC membrane was not good in terms of blood compatibility. When blood comes into contact with the hydroxyl groups of RC, complement 3 (C3) is activated and broken down into C3a and C3b. C3a attracts leukocytes into the alveoli and traps them, resulting in a transient decrease of leukocytes from the blood [1]. Therefore, an improvement was made to RC in which one, two, and/or all three hydroxyl groups (-OH) is/are masked

by corresponding number of acetyl groups (-$COCH_3$). They are called cellulose (mono-)acetate (CA or CMA), cellulose diacetate (CDA), and cellulose triacetate (CTA), depending on the number of acetyl groups introduced into the classic RC. CDA and CTA are still popular these days, while RC is no longer commercially available. All these cellulosic membranes have homogeneous or entirely uniform structures; however, a new CTA that has asymmetric structure, termed ATA® (Asymmetric Triacetate, Toyobo Co., Osaka, Japan) was developed and commercial dialyzers with ATA® are available from Nipro Co., Osaka, Japan). ATA® has an improved surface roughness by introducing new spinning technology that made it possible to present the skin layers on the surface. The surface roughness of the membrane affects platelet activity and adhesion. Then ATA® membrane was expected to have less protein adhesion than other CTA membranes; however, a study comparing the blood compatibility of CTA and ATA® showed little adhesion of platelets to either membrane [2]. The authors concluded that the CTA has already acquired excellent blood compatibility in clinical level.

AN69® Membrane

AN69® membrane was introduced in 1973; however, it had been first developed in 1969 by Rhone-Poulenc, France, and this fact was taken as a part of the brand name. AN69® is one of the copolymerized materials of PAN with acrylonitrile and methallylsulfonate groups, the latter group made AN69® as a strongly negative charged membrane, dropping out Na^+ from the group. When blood comes in contact with negatively charged AN69®, the coagulation factor XII and the complement may be activated. However, since complement C3a and C5a are positively charged, they are adsorbed onto AN69® membranes, making it difficult for complement to be activated any further. In 1990, it was reported that plasma C3a and C5a concentration was significantly decreased by AN69® [3]. Moreover, because amino groups of cytokines are positively charged, cytokines are ionically adsorbed to AN69® membranes. Therefore, dialyzers with AN69® are popular in treatment of acute kidney injury (AKI) with severe sepsis and septic shock. Incidentally, AN69® ionically adsorbs cytokines by electric charge, while PMMA adsorbs cytokines by trapping them on the surface as well as its inside structure.

PMMA Membranes

PMMA membranes are known to adsorb low molecular weight proteins (LMWPs) such as β2-microglobulin [4]. In past study, the 5-year survival rate of hemodialysis patients treated with PMMA was higher than those treated with PSf membranes [5]. It was deduced that the PMMA adsorbed and removed inflammatory LMWPs, which may have improved the survival rate. In recent years, PMMA has been further improved by introducing a new membrane surface processing technique (NF series, Toray Medical Co., Tokyo, Japan) that reduced the platelet adhesion. Although the NF series shows less platelet adhesion, the adsorption of LMWPs such as β2-microglobulin is comparable to conventional products [6]. It was inferred that the NF series exhibited better antithrombotic properties than conventional PMMA membranes because of reduced negative charge [6].

PSf/PES/PEPA Membranes

PSf is the most commonly used membrane worldwide because of its high water and solute permeabilities. There were, however, several reports of thrombocytopenia with the use of PSf membranes [7,8]. Moreover, dyspnea, hypotension, hypoxia, bronchospasm, chest pain, and abdominal symptoms were also reported in patients using PSf or PES [9]. Then improvements have been attempted to PSf. One of such trial was made by coating the membrane with vitamin E for the purpose of anti-inflammatory and antioxidant properties (Asahi Vitablen, Asahi Kasei Medical Co., Ltd., Tokyo, Japan). It is presumed that the antioxidant effect of vitamin E can prevent oxidation of the cell membrane of red blood cells. Vitamin E coated PSf may be useful for patients with high erythropoiesis stimulating agent tolerance [10]. Furthermore, it has also been reported that the use of PSf membranes coated with vitamin E significantly reduced total and LDL cholesterol levels [11]. Platelets do not directly adhere to PSf membrane; however, after fibrinogen adheres to the membrane, platelets adhere to fibrinogen on the membrane. Although all PSf membranes include polyvinylpyrrolidone (PVP) as a hydrophilic agent, a novel hydrophilic polymer has been introduced recently, expecting reducing platelet adhesion by decreasing protein attachment (NV series, Toray Medical Co., Tokyo, Japan). During hemodialysis, platelet-derived particles are released from platelets that have been activated by contact with the dialysis membrane. In a study comparing the NV series with normal PSf membranes from other companies, microparticles were significantly reduced in the NV series [12]. Platelets tend to release more microparticles when subjected to higher shear stress. However, it was presumed that the hydrophilic polymer inhibited the adhesion of platelets to the dialysis membrane, making the platelets less susceptible to shear stress and reducing generation of microparticles.

In a study comparing the degree of platelet adhesion to PMMA and to PSf membranes, little platelet adhesion was observed to PSf membranes, whereas activated platelet adhesion was significantly observed to PMMA [13]. PMMA is hydrophobic in nature, while PSf itself is also hydrophobic as a material but is hydrophilized by introducing PVP when casting the membrane. This result may be attributed to the

well-known fact that the hydrophilic dialysis membranes were more blood compatible than the hydrophobic ones.

Current PSf membranes are sterilized by autoclave, gamma-ray, or electron beam. It has been reported that hemodialysis using electronically sterilized dialysis membranes increases the risk of post-dialysis thrombocytopenia [14]. It was assumed that the electron beam irradiation may have changed the structure of the dialysis membrane, making it easier for platelets to be adsorbed onto the membrane. On the other hand, it has also been reported that there was no association between electron beam sterilization and thrombocytopenia [15]. A study comparing the blood compatibility of PSf membranes with autoclave and with gamma-ray irradiation found no significant difference in platelet adhesion to the dialysis membrane and decrease in platelet count [16]. Both sterilization methods could cause changes the structure of the membrane, but the degree of changing may be comparable.

PEPA membranes with no PVP and with various amount of PVP are available (Nikkiso Co., Ltd., Tokyo, Japan). Yamashita et al. reported that the higher the amount of PVP included in the membrane, the higher C3a elevation may be found during the treatment using PEPA with various PVP contents as well as PSf with much higher PVP contents [17]. They concluded that the PVP content may be another factor for evaluating biocompatibility.

Conclusion

In this article, we reviewed the history and current situations of blood compatibility of hemodialysis membranes. When selecting hemodialysis membranes, attention usually tends to be focused only on solute and water removal performance; however, blood compatibility also needs to be considered for a better success of dialysis therapy.

Author Contributions Statement

K.T. searched the literature, and prepared the article. A.C. Y. helped draft and review the manuscript.

Conflict of Interest Disclosure

None.

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