Renal Replacement Therapy

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In vitro evaluation of the platelet adhesion and interferon-γ production capacity of mononuclear cells coming in contact with a hydrophilic polymer-embedded polysulfone dialyzer

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Abstract

Background A polysulfone dialysis membrane containing both polyvinylpyrrolidone (PVP) and the novel hydrophilic polymer (NV polymer) has been developed in an attempt to modify the blood contact surface of the membrane. In the present study, we performed an in vitro evaluation of the NV polymer-embedded membrane (NV membrane), focusing on the adhesion of blood cells to the membrane and the interferon (IFN)-γ production capacity of peripheral blood mononuclear cells coming in contact with the membrane.

Methods Two membranes, the NV membrane and the conventional membrane embedded with PVP alone (CX), were evaluated simultaneously by dividing the porcine blood obtained from the same animal into two portions. The blood cell adhesion to the membranes was evaluated by measuring the hemoglobin concentrations and lactate dehydrogenase (LDH) activities in the eluates extracted from the membranes. The IFN-γ production capacity in response to phytohemagglutinin stimulation of mononuclear cells coming in contact with either membrane was evaluated.

Results Both the hemoglobin concentration and LDH activity, corrected by excluding erythrocytes from the eluate, were about 25% lower in the eluate from the NV membrane than in the eluate from the CX membrane. The IFN-γ production capacity of the mononuclear cells coming in contact with dialysis membrane remained unchanged for the case of the NV membrane, while it decreased for the case of the CX membrane.

Conclusions A lower degree of adhesion of blood cells to the membrane and a lower degree of reduction in the IFN-γ production capacity of mononuclear cells coming in contact with the membrane were observed for the NV membrane, as compared with the PVP membrane, which may suggest improved biocompatibility of the NV membrane.

Keywords Biocompatibility, Polysulfone dialysis membrane, Hydrophilic surface, Blood cell adhesion, Interferon-γ

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Introduction

Dialysis membranes with improved permeability and biocompatibility have been developed over the past few decades. The current trends in membrane development are toward modification of the blood contact surface to suppress platelet activation and the subsequent biological responses [1]. Many materials with improved biocompatibility have been developed in the field of biomaterials, but the mechanisms underlying the improved biocompatibility of these surfaces is not yet fully understood. Recently, mobility of the bound water to the polymer in the dialysis membrane was proposed as one possible mechanism [2, 3]. The development of a polysulfone dialysis membrane containing both polyvinylpyrrolidone (PVP) and the NV polymer, a hydrophilic polymer that has been demonstrated to show high mobility of the bound water to the polymer [4] (Toraylight® NV; Toray Medical Co., Ltd., Tokyo, Japan), is one such an attempt to modify the blood contact surface of the dialysis membrane. According to a previous small-scale study, this membrane induces less platelet activation, less platelet adhesion to the membrane [5], and less release of platelet-derived microparticles [6].

The clinical immunodeficiency state in patients undergoing hemodialysis, e.g., impaired response to vaccinations such as hepatitis B and tetanus vaccines [7, 8], is considered to be attributable to the bioincompatibility of dialysis membranes currently in use. Lower secretion levels of interferon (INF)-γ and interleukin-2 in response to stimulation were observed in leukocytes from patients undergoing hemodialysis as compared with those from healthy controls, in line with the reported changes in the helper T cell profile [9]. Decreased secretion of these cytokines in response to stimulation from leukocytes derived from patients undergoing hemodialysis can result in impaired cellular immune functions and impaired antibody production after vaccination. In vitro evaluation of the potential of leukocytes to secrete INF-γ in response to stimulation could be a useful method to evaluate the biocompatibility of a dialysis membrane in relation to the impaired immune status of patients undergoing hemodialysis. The biocompatibility of an NV polymer-embedded membrane (NV membrane) has not yet been investigated from this aspect, either in clinical studies or in in vitro experiments.

Eventually, the biocompatibility of a dialysis membrane should be assessed in clinical settings. However, it is often difficult to precisely clarify the biocompatibility of dialysis membranes in clinical settings, because both patient- and treatment-related factors, such as the pathological condition of the patient, treatment conditions, and the varying abilities of patients for coagulation or platelet activation, could have large effects on the results. It is useful, therefore, to perform complementary evaluations in vitro, for example, using porcine blood [1, 10]. Fresh porcine blood can be used for in vitro comparison of the adhesion of blood cells, as well as of the solute removal performance of two types of membranes, by dividing the blood obtained from the same animal into two portions [10].

The aim of the present study is to perform in vitro evaluation of the biocompatibility of the NV membrane from the aspects of adhesion of the blood cells to the membrane and change in the IFN-γ production capacity in response to phytohemagglutinin (PHA) stimulation of mononuclear cells coming in contact with the dialysis membrane.

Methods

Blood preparation

Fresh porcine blood was obtained from a dealer of animal blood and organs for research use (Tokyo Shibaura Zouki, Tokyo, Japan) on the morning of the experiments. After addition of sodium citrate at a final concentration of 10 mM, the blood was carefully transferred in a cooling box to our laboratory. At our laboratory, heparin (heparin sodium injection 50,000 units/50 mL, FUSO Pharmaceutical Industries Ltd., Tokyo, Japan) was added to the blood at a final concentration of 1000 U/L, followed by addition of penicillin and streptomycin (GIBCO, NY) at a final concentration of 100 units/mL and 100 μg/mL, respectively.

Dialyzer

Two types of dialyzers (dialysis membranes) were evaluated by the 4 h in vitro circulation experiment, which mimics the situation of blood circulation in a dialyzer during hemodialysis treatment; one was the conventional polysulfone dialyzer (Toraylight® CX-16U, Toray Medical Co., Ltd., Tokyo, Japan), composed of a polysulfone membrane with only PVP embedded as a hydrophilic agent (CX membrane), while the other, also a polysulfone dialyzer (Toraylight® NV-16U, Toray Medical, Tokyo, Japan), was a polysulfone membrane containing both PVP and the NV polymer, a novel hydrophilic polymer, which has been demonstrated to show a high mobility of the bound water to the polymer (NV membrane) [4]. The technical specifications, including the membrane area, hollow fiber diameter, and thickness, effective length, blood side volume, and water permeability, were nearly identical between the two types of dialysis membranes (Table 1).

Circulation experiment

Two sets of experiments were carried out using blood obtained from the same animal divided into two portions

Table 1 Technical specification of dialyzer used

	CX-16U	NV-16U
Membrane material	Polysulfone	
Membrane areas (m^2)	1.6	
Hollow fiber diameter (μm)	200	
Hollow fiber thickness (μm)	40	
Effective length (cm)	26.3	
Blood side volume (mL)	93	100
Water permeability [mL/(h Pa m^2)]	0.068	0.063

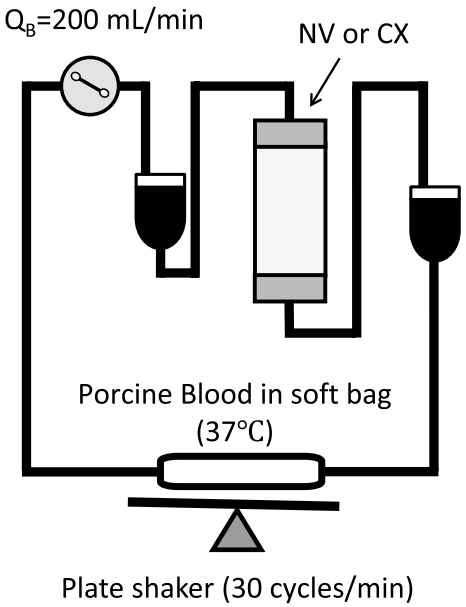

Fig. 1 Schematic diagram of the experimental circuit

to compare the two membranes, namely, the CX membrane and the NV membrane. After priming the inner and outer sides of the dialyzer with saline, the saline was replaced with blood, and the blood-side outlet was connected to a soft bag (FCB-3, Asahi Kasei Kuraray Medical, Tokyo, Japan). The blood was allowed to flow into the soft bag until the total volume of blood inside the circuit, dialyzer and soft bag reached 1 L. The soft bag was placed on a plate shaker, covered with a water jacket containing circulating water at 42 °C to maintain it at a constant temperature (37 °C), and shaken at 30 cycles/min. The blood flow rate, Q_B was set at 200 mL/min (Fig. 1).

During the blood circulation, the blood was collected every hour to check the blood cell counts (platelet and leukocytes) and hematocrit level. The sampled blood was diluted 1:1 with phosphate-buffered saline (0.1 M phosphate, pH 7.4) containing 0.5 mM ethylenediamine tetraacetic acid disodium salt dehydrate, and the platelets and leukocytes were counted with a hematology analyzer for animal blood (Celltac α MEK-6450, Nihon Kohden Co., Tokyo, Japan).

Evaluation of blood cell adhesion

To compare the adhesions of erythrocytes and the other cells, an isolated erythrocyte saline solution was prepared by repeated centrifugation (500 rpm) and replacement of the platelet-rich plasma with saline 4 times, and relationship between the hemoglobin concentration and LDH activity for erythrocytes was determined using 3 different blood samples. The LDH activity corrected by excluding erythrocytes was also determined by subtracting LDH activity of erythrocytes calculated by the relationship between hemoglobin concentration and LDH activity of erythrocytes from the LDH activity of all cells.

The blood cell adhesion to the membranes was evaluated by a previously described method [8]. In brief, after the circulated blood was washed out from the dialyzer using 1.5 L of saline in the single pass mode (flow rate of 100–150 mL/min), 200 mL of saline containing 0.5% TritonX-100 (polyoxyethylene-*p*-isooctylphenol, Wako Pure Chemical, Tokyo, Japan) was circulated through the dialyzer at a Q_B of 100 mL/min for 2 h, in an attempt to break the blood cells adhering to the membrane and elute the proteins in the cells. The hemoglobin concentration in the eluate was measured by spectrophotometry (absorbance at 580 nm), and the lactate dehydrogenase (LDH) activity in the eluate was measured using a LDH detection kit [cytotoxicity detection kit (LDH), Roche Applied Science, Penzberg, Germany]. The LDH activity was calibrated by the LDH activity of human erythrocyte origin (Enzyme Calibrator, Wako Pure Chemical, Tokyo, Japan).

Evaluation of the IFN-γ production capacity of mononuclear cells

The IFN-γ production capacity in response to PHA stimulation was evaluated for mononuclear cells that had come in contact with each of the dialysis membranes and for cells that had not come in contact with either dialysis membrane (control). The mononuclear cells were collected from the blood using lymphoprep™ (Axis-Shield PoC AS, Oslo, Norway), by the specific gravity centrifugal method. The mononuclear cell suspension was adjusted to a density of 2.5×10^5 cells/mL using RPMI1640 (GIBCO, NY) containing 20 v/v% of the plasma separated from blood that had circulated through each of the dialyzers. PHA(PHA-L, Calbiochem®, Merck KGaA, Darmstadt, Germany) was added to the cell suspension at a final concentration of 20 μg/mL and the cells were cultured for 48 h. After 48 h of culture, the concentrations of IFN-γ in the supernatants of the cell suspensions obtained by centrifugation were measured using

the IFN-γ Swine ELISA Kit (KSC4022; Invitrogen, CA), in accordance with the manufacturer's instructions. In brief, the wells of microtiter strips coated with a monoclonal antibody specific for swine IFN-γ were used. The supernatants and standard solutions with known IFN-γ concentrations were pipetted into these wells, followed by the addition of a biotinylated monoclonal antibody as a second antibody and incubation. After removal of the excess second antibody, streptavidin–peroxidase was added, followed by further incubation. After all the unbound enzymes were removed, a substrate solution was added. The intensity of the colored product was measured using a microplate reader (model 680, Bio-Rad Laboratories, Inc., CA) at a wavelength of 460 nm (reference wavelength 655 nm).

Statistical analysis

The Smirnov–Grubbs test was used to check for outliers of the hemoglobin concentration, LDH activity, and IFN-γ concentration. The statistical significance of differences in the hemoglobin concentration and LDH activity were determined by the Wilcoxon matched-pair signed-rank test, and the statistical significance of differences in the IFN-γ concentration was determined by the Freidman test. The differences with probability values (p-value) of less than 0.05 were considered as being statistically significant.

Results

To confirm the absence of technical errors, such as sedimentation of blood cells in the soft bag, platelet consumption, and other errors in the experiment, we measured the platelet and leukocyte counts and hematocrit levels during the 4 h circulation experiment (Fig. 2) and confirmed the absence of any changes with time during the circulation experiment for either membrane. Furthermore, no significant differences in these parameters were observed between the CX membrane and NV membrane either.

To quantitatively compare the number of erythrocytes adhering to the two membranes, the hemoglobin concentration of the eluate from the dialyzer after blood circulation for 4 h was measured (Fig. 3a). A saline solution containing 0.5% TritonX-100 was used to break the blood cells adhering to the membrane and elute the proteins, such as hemoglobin, LDH, etc., from the membranes. The hemoglobin concentration in the eluate from the NV membrane was significantly lower than that in the eluate from the CX membrane, suggesting that the number of erythrocytes in the clots formed on the NV membrane was lower than that in the clots formed on the CX membrane. To compare the total number of adherent blood cells between the two membranes, the LDH activity in the eluate from the dialyzers after blood circulation for 4 h was measured (Fig. 3b). The LDH activity in the eluate from the NV membrane was significantly lower than that in the eluate from the CX membrane, suggesting that the number of cells adhering to the NV membrane was lower than that adhering to the CX membrane. Both the hemoglobin concentration and LDH activity in the eluate from the NV membrane were about 25% lower than those in the eluate from the CX membrane.

The relationship between the hemoglobin concentration and uncorrected LDH activity also revealed a lower blood cell adhesion to the NV membrane (Fig. 4a). The analysis using washed erythrocytes revealed that about 0.2 U/L of LDH was contained in erythrocytes with a hemoglobin content of 1 g/dL. Based on this determined relationship, the corrected LDH activity was calculated by excluding the erythrocyte LDH activity (Fig. 4b). In

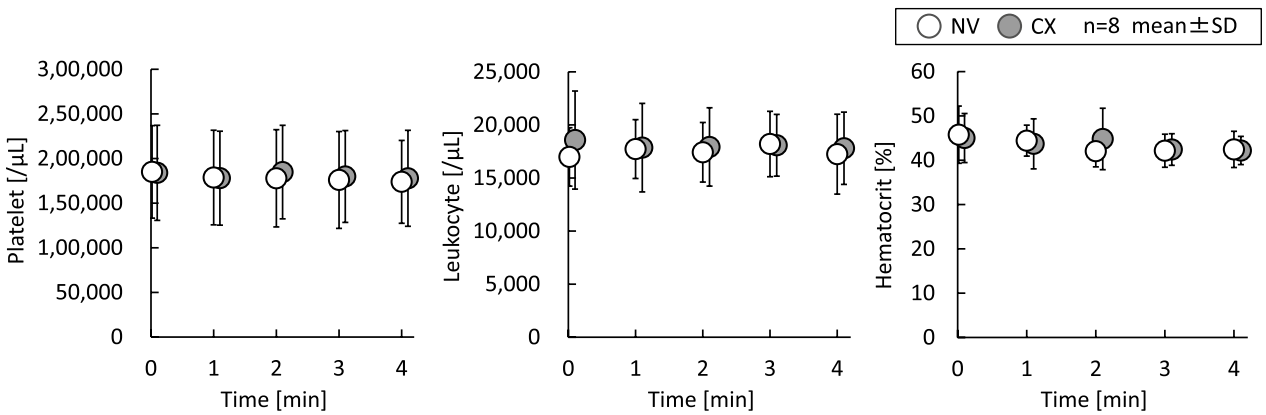

Fig. 2 The platelet and leukocyte counts and hematocrit levels were measured during 4 h blood circulation. These parameters did not change during the blood circulation for either membrane. Furthermore, no significant differences in these parameters were observed either between the NV polymer-embedded polysulfone membrane (NV membrane) and conventional PVP-embedded polysulfone membrane (CX membrane)

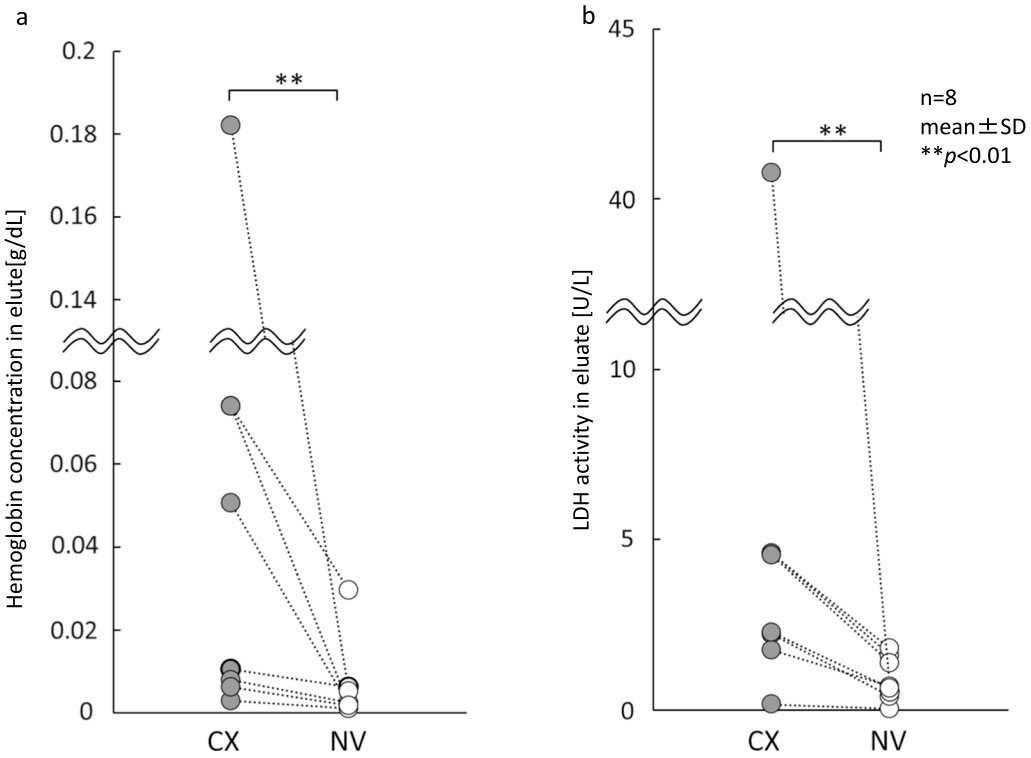

Fig. 3 **a** Hemoglobin concentration in the eluates from the dialyzers after 4 h circulation. **b** The lactate dehydrogenase (LDH) activities in the eluates from the dialyzers after 4 h blood circulation. The paired data are connected by dotted lines. The hemoglobin concentration and LDH activity in the eluate from the NV membrane was significantly lower than that in the eluate from the CX membrane, suggesting that the numbers of cells in the clots formed on the NV membrane were lower than those on the CX membrane

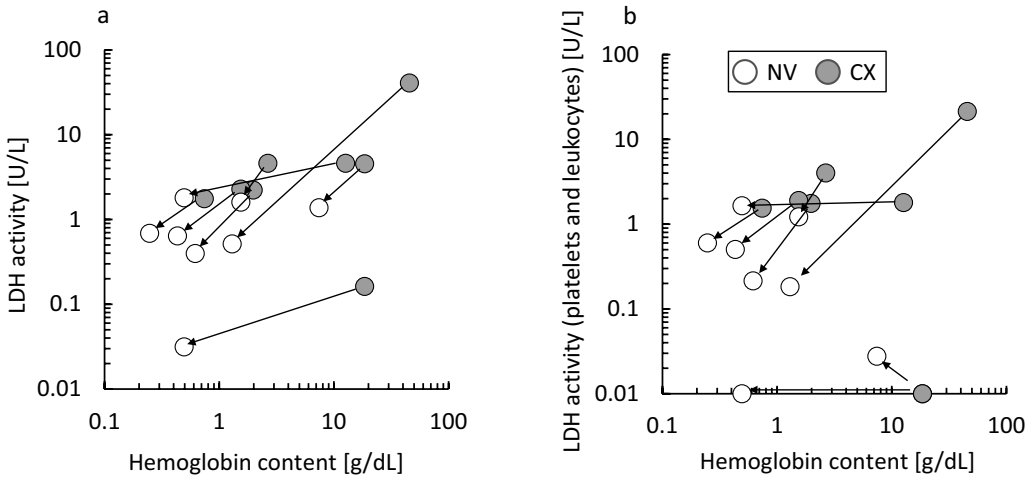

Fig. 4 **a** Relationship between the hemoglobin concentration and LDH activity for all blood cells showed the low blood cell adhesion of the NV membrane compared with the CX membrane. **b** The hemoglobin concentration and corrected LDH activity, calculated by excluding erythrocytes from the eluate, showed that the numbers of both erythrocytes and other cells (platelets and/or leukocytes) adhering to the NV membrane were lower than those to the CX membrane in five cases, and only the numbers of erythrocytes adhering to the CX membrane were lower as compared with that of the cells adhering to the NV membrane in the other three cases

five cases, the numbers of both erythrocytes and other cells (platelets and/or leukocytes) adhering to the NV membrane were lower than those adhering to the CX membrane. In the remaining three cases, the number of adherent erythrocytes was lower for the CX membrane as compared with the NV membrane. In two of these latter cases, the numbers of platelets and/or leukocytes adhering to the both CX and NV membranes were also very low.

Lastly, the IFN-γ production capacity in response to PHA stimulation was evaluated for the mononuclear cells that had come in contact with each of the dialysis membranes and cells that had not come in contact with either dialysis membrane (Fig. 5). While there was no significant difference in the IFN-γ production capacity in response to PHA stimulation between the mononuclear cells that had come in contact with the NV membrane and the control cells, the IFN-γ production capacity of the cells that had come in contact with the conventional CX membrane was significantly lower as compared with that of the control cells.

Discussion

The main findings of this study are that (1) the adhesion of blood cells was lower for the NV membrane than for the conventional CX membrane, and (2) the IFN-γ production capacity in response to PHA stimulation of mononuclear cells that had come in contact with the dialysis membrane remained unchanged for the case of the NV membrane but decreased significantly for the case of the conventional CX membrane.

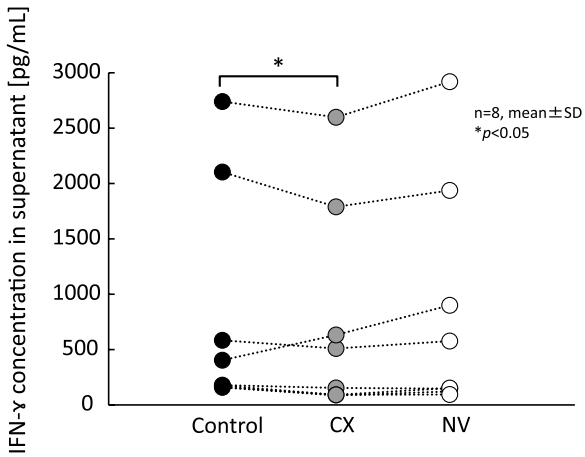

Fig. 5 IFN-γ production capacity in response to phytohemagglutinin (PHA) stimulation of peripheral blood mononuclear cells that had come in contact with each of the dialysis membranes. The paired data are connected by dotted lines. The IFN-γ production capacity in response to PHA stimulation of mononuclear cells that had come or not come (control) in contact with the membranes was evaluated for each of the dialysis membranes. While the IFN-γ productivity of the mononuclear cells that came in contact with the membrane did not differ significantly from that of the control cells for the case of the NV membrane, it was significantly lower than that of the control cells for the case of the CX membrane

In the present study, the values of one of the CX membrane data for the Hb concentration and LDH activity in the eluate were much higher as compared with the other data and were determined to be outliers ($p < 0.001$) (Fig. 3). However, there was no justification to exclude the outlier data, because there were no unusual manipulations in the experiment. All measurements had been performed simultaneously, and the outlier values were actually found for the dialyzer that had more residual blood. Therefore, all data, including the results of statistical analysis using all the data, are presented in Fig. 3. On the other hand, the Wilcoxon matched-pair signed-rank test was also performed after excluding the outliers; the conclusion was the same, as the Hb and LDH activity values in the eluate were significantly lower ($p < 0.05$) for the NV membrane as compared with the CX membrane.

The number of erythrocytes in the clots formed on the NV membrane was lower than that in the clots formed on the CX membrane. Erythrocytes cannot adhere to the membrane surface alone; therefore, it is considered that erythrocytes adhere via fibrin to the membrane, forming red cell thrombi. This result indicates that the NV polymer may suppress fibrin formation due to activation of the coagulation system or suppress fibrin adhesion to the membrane. In more than half cases, not only the number of erythrocytes but also the number of other cells (platelets and/or leukocytes) adhering to the membrane were lower for the case of the NV membrane than for the case of the CX membrane. NV polymer is also reported to adsorb less fibrinogen [10], which might prevent the formation of fibrin to incorporate erythrocytes, leukocytes, and platelets.

In regard to the platelet adhesion, three different types of experiments to confirm the effects of the NV membrane on platelets have been carried out, including the experiment in the present study. In the experiment in the basic research field of material sciences, the NV membrane showed reduced platelet adhesion as compared with a conventional PVP-embedded polysulfone dialyzer [4], although it was carried out under nonflow conditions. The experiment carried out in a clinical setting [5] revealed a lower degree of platelet adhesion on the NV membrane as compared with the CX membrane, although this was only a small-scale study, and many patient- and treatment-related factors could have potentially affected the data. The present in vitro study, which was carried out under flow conditions very similar to the clinical setting, also demonstrated lower adhesion of blood cells, including platelets, to the NV membrane as

compared with the CX membrane. Although, the study had the limitation of the porcine blood used having been purchased from a commercial vendor [11]. On the basis of the aforementioned evidence, it would be rational to conclude that the NV polymer can inhibit platelet adhesion to the NV membrane.

A lower production capacity of INF-γ in response to PHA stimulation has been observed in peripheral blood mononuclear cells obtained from hemodialysis patients as compared with those obtained from healthy controls, which has been attributed to the reduced activation of T cells overall and a skewed differentiation pattern of helper T cells (Th) toward the Th1 direction [9]. In the present study, cell contact with the CX dialysis membrane, through blood circulation for 4 h, reduced the INF-γ production capacity of mononuclear cells in response to PHA stimulation, probably due to a lower degree of activation of mononuclear cells during circulation. The INF-γ production capacity of mononuclear cells in response to PHA stimulation following blood circulation for 4 h remained unchanged for the case of the NV membrane. These results also indicate that in vitro evaluation of INF-γ production capacity of mononuclear cells in response to PHA stimulation might be a useful method to evaluate the cellular immune functions.

Previous studies have demonstrated mutual interactions between platelets and leukocytes [12, 13]. It is also known that activated platelets bound to neutrophils promote the generation of superoxide anions by the neutrophils [14–16]. In turn, leukocytes and leukocyte-released superoxide anions enhance platelet adhesion [17, 18]. Therefore, both platelet and leukocyte activations that could be triggered by contact with the dialysis membrane surface should be reduced to improve the biocompatibility of a membrane. In the present study, only two aspects of blood cell activation (blood cell adhesion and INF-γ production capacity of mononuclear cell in response to PHA stimulation) were investigated under the condition where mutual interactions existed. In vitro experiments have shown reduced platelet activation and neutrophil activation following direct interaction of the cells [10] and reduced formation of platelet-neutrophil complexes induced by membrane contact [19] for the NV membrane as compared with the conventional CX membrane. Thus, the NV membrane surface appears to have few direct effects on the platelets and neutrophils. Since IFN-γ production by mononuclear cells coming in contact with the NV membrane remained unchanged in the present study, the NV membrane surface may appear to have few direct effects on mononuclear cells, including T cells, as well.

The relative lack of influence of the blood cell type on the direct effects of contact with the dialyzer on the cells for the case of the NV membrane suggests that in addition to the chemical composition of the membrane, physical properties, such as smoothness and softness of the membrane surface, also possibly influence the interaction of blood cells with the dialysis membrane. The NV membrane, which contains NV polymer in addition to PVP, has been shown by atomic force microscopy to have a relatively smooth membrane surface and a thicker soft layer on the inner surface (CX membrane (PVP) 5 nm, NV membrane (PVP + NV polymer) 13 nm) [4]. Previous studies have reported that NV polymers exhibit higher bound-water mobility [4] and lower protein adsorption, particularly of fibrinogen [4, 10]. This could explain the lower occurrence of red cell thrombi on NV membranes observed in this study. The relatively smooth surface of the membrane and the thicker soft layer on the inner surface of the NV membrane could explain the suppressed biological responses of the platelets and mononuclear cells and also why the production of IFN-γ triggered by membrane-blood contact was maintained. A further detailed investigation is required to clarify the effects of the chemical and physical properties of the dialysis membrane on the blood cells coming in contact with the membrane, which could pave the way for the eventual development of a novel membrane with improved biocompatibility.

We demonstrate in the present study that the NV membrane showed improved biocompatibility, with reduced platelet adhesion/activation and maintained IFN-γ production capacity of mononuclear cells in response to PHA stimulation. Although it remains unclear whether these improvements are due to the chemical structure of the NV polymer or to the physical properties of the modified membrane, these in vitro results indicate that the NV polymer-embedded polysulfone membrane-blood interaction was associated with less stimulation of the blood cells. It is not clear at this time if these results will translate into clinical benefits, as a variety of biological responses interacting with each other occur in the clinical setting. We propose to clarify the effect of NV polymer-embedded membranes in clinical practice in the future by confirming the biological responses caused by platelet activation, in particular, and the effect of reduced stimulation of mononuclear cells.

In the present study, we circulated only blood through the blood circuit and dialyzer, without using dialysate or performing ultrafiltration. The aim is to examine the interaction between the membrane and blood cells. Further experiments using dialysate and ultrafiltration will provide clearer information on factors influencing the membrane biocompatibility in clinical practice. This, in turn, will lead to the development of better membranes and feedback for clinical practice.

Conclusions

Our in vitro evaluations revealed a lower adhesion of blood cells to the NV membrane and also that the IFN-γ production capacity in response to PHA stimulation of mononuclear cells coming in contact with the dialysis membrane remained unchanged for the case of the NV membrane but decreased significantly for the case of the CX membrane.

Abbreviations

INF	Interferon
LDH	Lactate dehydrogenase
PHA	Phytohemagglutinin
PVP	Polyvinylpyrrolidone
Q_B	Blood flow rate

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Author contributions

Y.K. and Ko.Ko. designed the research, performed the experiment and the data analysis, and wrote the manuscript; S.U. and H.T. designed the research and performed the experiment; Ke.Ko., K.S., M.K., and H.K. provided the working hypothesis, participated in the research design, and substantially contributed to the study concept.

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Availability of data and materials

The datasets analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Research Grant from Toray Industries, Inc. SU is currently working at Toray Industries, Inc.

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References

1. Kokubo K, Kurihara Y, Kobayashi K, Tsukao H, Kobayashi H. Evaluation of the biocompatibility of dialysis membranes. Blood Purif. 2015;40:293–7.
2. Tanaka M, Mochizuki A, Ishii N, Motomura T, Hatakeyama T. Study of blood compatibility with Poly(2-methoxyethyl acrylate). Relationship between water structure and platelet compatibility in Poly(2-methoxyethylacrylate-co-2-hydroxyethylmethacrylate). Biomacromol. 2002;3:36–41.
3. Miwa Y, Tanaka M, Mochizuki A. Water structure and polymer dynamicas in hydrated blood compatible polymer. Koubunshi Ronbunshu. 2011;68:133–46.
4. Ueno Y, Fujita M, Sugaya H. Dialysis membrane with hydrophilization of the structure around its surface (article in Japanese). Membrane. 2011;37:17–21.
5. Yamaka T, Ichikawa K, Saito M, Watanabe K Nakai A, Higuchi N, et al. Biocompatibility of the new anticoagulant dialyzer TORAYLIGHT® NV. Science Postprint. 2014;1:e00020.
6. Hidaka S, Kobayashi S, Maesato K, Mochida Y, Ishioka K, Oka M, et al. Hydrophilic polymer-coated polysulfone membrane improves endothelial function of hemodialysis patients: A Pilot Study. J Clin Nephrol Res. 2015;2:1020.
7. Köhler H, Arnold W, Renschin G, Dormeyer HH, Meyer zum Büschenfelde KH. Active hepatitis B vaccination of dialysis patients and medical staff. Kidney Int. 1984;25:124–8.
8. Girndt M, Pietsch M, Köhler H. Tetanus immunization and its association to hepatitis B vaccination in patients with chronic renal failure. Am J Kidney Dis. 1995;26:454–60.
9. Sester U, Sester M, Hauk M, Kaul H, Köhler H, Girndt M. T-cell activation follows Th1 rather than Th2 pattern in haemodialysis patients. Nephrol Dial Transplant. 2000;15:1217–23.
10. Koga Y, Fujieda H, Meguro H, Ueno Y, Aoki T, Miwa K, et al. Biocompatibility of polysulfone hemodialysis membranes and its mechanisms: involvement of fibrinogen and its integrin receptors in activation of platelets and neutrophils. Artif Organs. 2018;42:E246–58.
11. Kokubo K, Kurihara Y, Tsukao H, Maruyama N, Kobayshi K, Shinbo T, et al. Effects of increased surface coverage of polyvinylpyrrolidone over a polysulfone hemofilter membrane on permeability and cell adhesion during continuous hemofiltration. J Artif Organs. 2015;18:257–63.
12. Bazzoni G, Dejana E, Del Maschio A. Platelet-neutrophil interactions. Possible relevance in the pathogenesis of thrombosis and inflammation. Haematologica. 1991;76:491–9.
13. Li N, Hu H, Lindqvist M, Wikstrom-Jonsson E, Goodall AH, Hjemdahl P. Platelet-leukocyte cross talk in whole blood. Arterioscler Thromb Vasc Biol. 2000;20:2702–8.
14. Nagata K, Tsuji T, Todoroki N, Katagiri Y, Tanoue K, Yamazaki H, et al. Activated platelets induce superoxide anion release by monocytes and neutrophils through p-selectin (CD62). J Immunol. 1993;151:3267–73.
15. Nagata K, Tsuji T, Hanai N, Irimura T. Role of o-linked carbohydrate chains on leukocyte cell membranes in platelet-induced leukocyte activation. J Biol Chem. 1994;269:23290–5.
16. Tsuji T, Nagata K, Koike J, Todoroki N, Irimura T. Induction of superoxide anion production from monocytes an neutrophils by activated platelets through the p-selectin-sialyl lewis x interaction. J Leukoc Biol. 1994;56:583–7.
17. Salvemini D, de Nucci G, Sneddon JM, Vane JR. Superoxide anions enhance platelet adhesion and aggregation. Br J Pharmacol. 1989;97:1145–50.
18. Tsukao H, Kokubo K, Takahashi H, Nagasato M, Endo T, Iizuka N, et al. Activation of platelets upon contact with a vitamin E-coated/non-coated surface. J Artif Organs. 2013;16:193–205.
19. Koga Y, Meguro H, Fujieda H, Ueno Y, Miwa K, Kainoh M. A new hydrophilic polysulfone hemodialysis membrane can prevent platelet–neutrophil interactions and successive neutrophil activation. Int J Artif Organs. 2019;42:175–81.

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