Original article

EFFECT OF POLYETHERSULFONE COMPARED TO CELULLOSE DIACETATE DIALYZER MEMBRANE ON SERUM INTERLEUKIN-6 AND C-REACTIVE PROTEIN LEVES IN HEMODIALYSIS

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ABSTRACT

Synthetic dialyzer membrane is considered to have greater biocompatibility properties than cellulose based dialyzer membrane. This study is aiming to determine whether the use of polyethersulfone synthetic dialyzer (PES) membrane produce lower inflammatory (IL-6 and CRP) response compared to celullose diacetate (CDA).

Study samples were selected consecutively from all kidney failure patients who were undergoing routine HD at HD centers in Denpasar Mayoralty. Thirty HD patients consisted of 15 with PES (11 males and 4 females, aged 45 ±10 years) and 15 patients with CDA (8 males and 7 females, aged 48 ±13 years) were included in this study.

A significant increase of plasma IL-6 per 1000 monocytes (Z=-4.103, p=0.003), from18.56±21.00 pg/dl before HD to 56.00±105.41 pg/dl after HD among two groups was found. When the increase of plasma IL-6 per 1000 monocytes during hemodialysis was compared bewteen the two groups, a significant higher increase of plasma IL-6 per 1000 monocytes in CDA group compared to PES group (71.47±142.51 pg/dl versus 3.38±4.46 pg/dl, Z=-2.883, p=0.003). There was no significant increase of plasma hs-CRP levels before-after HD among both groups. Also, there was no significant difference of plasma hs-CRP changes during HD between the two groups. Using multivariate ANCOVA, a consistent effect between the two membrane (F=18.401, p=0.000) on logistic transformed of plasma IL-6 per 1000 monocytes changes. However, this effect was not significant (F=1.937, p=0.176) on logistic transformed of plasma hs-CRP changes. It was found that plasma levels of pre HD albumin related to logistic transformed of plasma IL-6 per1000 monocytes (F=5.610, p=0.026), however, there were no relationship between HD factor (KT/V) and HD age (months), with logistic transformed of plasma IL-6 per 1000 monocytes changes.

Increament of plasma IL-6 levels per 1000 monocytes during HD is smaller, however, changes of plasma hs-CRP levels during HD is similar among HD patients with PES than CDA membrane. In addition, plasma levels of pre HD albumin may affect plasma IL-6 changes during HD.

Keywords: polyethersulfone, celullose diacetate dialyzer membrane, interleukin-6, hs-CRP, hemodialysis

INTRODUCTION

Prevalence of ESRD (end-stage renal disease) who undergoing routine HD (hemodialysis) is increasing both in developed and developing countries ranging four to 254 per million population.[1] In Indonesia, prevalence of ESRD is estimated 350 per million (ASKES, unpublished).

Malnutrition is the earliest clinical problem in patients with reduced kidney function. Around 20 – 60% patients with HD had malnutrition.[2] Other study reported that prevalence of malnutrition among HD patients was 23 – 76%.[3] It was also reported that among HD patients 37.5% had malnutrition, mostly (21.4%) mild malnutrition.[4] Malnutrition which is characterized by hypoalbuminemia is a strong predictor of death in HD patients.[5]

The major mortality of HD patients is not due to malnutrition, however, mostly caused by CVD (cardiovascular disease), about 50% HD patients died due to CV disease6. The risk of CV death in patients with CKD (chronic kidney disease) at the age of 40 years was 100 times higher than normal population.[7] CV death contributed around 20 – 23% of annual mortality rate in United State.[8,9] Using ABPI (ankle-brachial index of pressure), it was reported that prevalence of POAD (peripheral obstructive arterial disease) was 15.2%.[10] In predialytic stage there was strong relationship between atheroasclerotic disease and malnutrition.[11] CRP levels a marker for inflammation is closely related to proinflammatory cytokines such as IL-1 dan TNF α.[12] In dialytic stage, the increased of CRP was reported a predictor of CVD.[13-15] Acute phase response may be responsible for atherogenic process.[16]

Hemodialysis is aiming to purify blood from the excess of substances which accumulate as subsequent reduced kidney function using semipermeabel membrane[17]. HD can induce inflammation, since it may activate complement system and leucocytes. The ability of dialyzer membrane to minimally induce inflammation is called biocompatible. Cellulose based mambrane is made from cotton activates complement system in-vitro, therefore, it is a bio-incompatible membrane. Synthetic polymer membranes, such as polysulfone, do not have polysaccharide chain, and does not activate complement in-vitro. This type of membrane can therefore reduce inflamatory response and called biocompatible.[18-20] In 2005 a prelemminary study done by us among patients with regular HD using cellulose diacetate dialyzer membrane in HD Unit Sanglah General Hospital. We reported that out of among 58 patients 38% had inflammation.[21] Inflammtory response may resposible to long term clinical outcomes in HD. In a meta-analysis study pre-dialytic ß2 mikroglobulin levels (amyloid substance) were lower and albumin levels was higher among patients using synthetic membranes than cellulose besed membranes.[22] The mechanism of in-vitro inflammtion in unmodified cellulose membrane using monocyte culture was reported by some authors.[23,24] An in-vivo study about the mechanism of membrane biocompatibilty has reported that unmodified cellulose membranes induced inflammation and acute phase response greater than synthetic polysulfone membrane.[25]

This study is aiming to determine whether inflammatory response measured by changing in serum IL-6 per 1000 monocytes and serum hs-CRP before-after HD is lower during HD using synthetic dialyzer (polyethersulfone) in comparison with cellulose based membrane (cellulose diacetate).

PATIENTS AND METHODS

A pre test-post test control group design was used in this study to observe difference in changes of serum IL-6 per 1000 monocytes and hs-CRP (before-after HD) as inflammatory response by polyethersulfone in comparison with cellulose diacetate dialyzer membrane.
ESRD patients who underwent HD in HD Units all over the city of Denpasar were included in this study. Those who were willing to participate in the study by filling in informed consent. ESRD patients were undergoing HD twice a week (5 hours each) for 3 months or more and in stable condition, aged 18 – 60 years were included in this study. HD patients who had sepsis, fever, congestive heart failure, malignancy, those on steroid or non-steroid anti-inflammatory drugs or cytotoxic drugs were excluded from this study. Eligible subjects were consecutively selected until number of subjects needed were met.

Chronic kidney disease is kidney damage which has ocurred for 3 months or more which is manifested as structural and/or functional abnormalities of the kidneys with or without reduction in GFR. Kidney failure is a condition in which GFR less than 15 ml/menit/1.73 m2 body surfase area, that frequently accompanied by signs and symtoms of uremia, and needed dialysis or

kidney transplatation therapy. Hemodialysis is a kind of kidney substitution therapy by a mean of purifying the blood from uremic substances by dialisate through semi-permeable membrane (dialyzer). Duration of hemodialysis therapy is the period between the first HD session and the study hemodialysis session. Duration of hemodialysis session is the period between the start of study HD session and the end of study HD session. Stable hemodialysis is hemodialysis which is taking places for 3 months or more. During this period the patients generally had minimal complication during HD. In addition, dry body weight as a target weight is gererally reached and patient's quality of life is recovered. Biocompatible membrane is a membrane which has the ability to minimally activate complement system and leucocytes, *invitro*. Synthetic polymer polyethersulfone membrane is classified as biocompatible membrane (Boure & Vanhoulder, 2004). Bio-incompatible membrane is a membrane that has greater ability to activate complement system and leucocytes, invitro. Cellulose based (cellulose diacetate) membrane is classified as bio-incompatible membrane (Boure & Vanhoulder, 2004). Age is determined by evaluating birth date in ID patients upto the the patients hospital admission. Gender is determined as phenotypic appearance of the subjects. Cellulose diacetate dan polyethersulfone dialyzer. Cellulose diacetate Dialyzer FB-110T was supplied by Nipro Corporation 3-9-3, Honjo-Nishi, Kita-Ku, Osaka, Japan. Polyethersulfone Surelyzer™ PES-130DH was supplied by oleh Nipro Corporation 3-9-3, Honjo-Nishi, Kita-Ku, Osaka, Japan. Questionnaire and medical records explored demmographic factor (age, gender), etiology of kidney disease (chronic glomerulonephritis, obstruction and infection, diabetes mellitus, or hypertension) concommitant disease (coronary arterial disease, or stroke), lab data (CBC, pre and post-HD urea levels and creatinine, albumin, CRP and IL-6) and co-treatments (steroid, NSAID and cytotoxic drugs).

Interleukin-6 levels were examined using serum samples that stored in a stable temperature of -20^0 C. Serum samples were collected until the number of samples was met and kits were opened and assay was done. Sandwich enzyme immunoassay, using Quantizing HS immunoassay kit which is produced by R&D System Inc. 614 McKinley N.E. Minneapolis, MN 55413 USA was used to examine IL-6 levels. High sensitivity-CRP were examined using serum samples that stored in a stable temperature of -20^0 C. Serum samples were collected until the number of samples were met and kits were opened and the assay was done. Immunometric assay (Immulite 2000®) was used to determined hs-CRP levels. Albumin levels were examined using Bromocresol purple. Pre-HD Hand grip strength was done on the hand with no arteriovenous (A-V) shunt, using Harpenden dynamometer (kg force). The measurement was done thrice and the highest value was used. Mid-arm muscle circumference (MAMC) was calculated by formula: MAMC = AC – (3,14 X TSF). Mid-arm circumference (AC), is measured at the middle of right upper arm. Triceps skin fold (TSF) is the skin fold on triceps muscle which measured using Harpenden calyper. Body mass index was calculated using formula: BMI = (BW, kg)/(heigh^2, m^2). The study was carried out at HD Unit Puri Raharja Hospital and Sanglah General Hospital Denpasar. Laboratory examinations were done at Research and Development Institute Prodia Laboratory Jakarta.

Sample size was calculated using two teatments with numeric scale outcome variable.[26] Using data by Schouten, at el.[25] 2000, who reported IL-6 levels on CU (cellulose based membrane) group, post-HD 10.9 pg/ml (SD: 7.9 pg/ml) and IL-6 levels on PS (synthetic membrane) group, post-HD 2.8 pg/ml, and typi-1 error (α) was set 5%, zα = 1.96; and type-2 error (β) was set 20%; zβ = 0,842, sample size was 13 (each groups), and rounded to 15. K-S (Kormogorov-Smirnov) test was used to test the normalty of continuous data. Logistic transformation may be performed to get normally dis-

tributed data. Nominal data was displayed using frequency data. Characteristics of subjects were analysed using descriptive statistics, including mean (standard deviation), frequency, median (inter-quartile). Levene test was used to test the homogeneity of continuous data. Appropriate comparison t test was used with regard to Levene test results. Parametric test was used for normally distributed continuous data. Independent student's t test was done to test the hypothesis of whether mean between the two independent groups are. Non-parametric statistics (Mann-Withney U and Wilcoxon rank tests) with median (inter-quartile) were used to test hypothesis of difference in non-continuous data between two independent groups. Multivariate (ANCOVA) analysis was used to control confounding variables, in order to have real effect of interventional variable against dependent variable. Level of significance (α) was set on probability (p-value) less than 0.05.

RESULTS

Thirty patients consisted 15 with polyethersulfone (PES) dialyzer (11 males; 4 females, aged 45 years) and 15 patients with cellulose diacetate (CDA) dialyzer (8 males; 7 females, aged 48 years) included in this study. Demographic characteristics, nutritional status, dialyzer and HD characteristics, and hematological profiles were shown on tables 1, 2 and 3. Some variables at baseline were not comparable in both groups.

Table 1. Baseline characteristics of subjects in PES and CDA groups

Baseline demographic and nutritional status	PES group (n=15) Mean±SD/ Frequency	CDA group (n=15) Mean±SD/ Frequency	P-value
Gender (M/F)	11/4	8/7	0.256
Age	45±10	48±13	0.450
Ethnicity			
Balinese	14	12	0.283
Javanese	1	3	
Etiology			
Chronic pyelonephritis	5	7	0.493
Chronic glomrulonephritis	8	8	
Diabetes mellitus	1	0	
Polycystic kidney disease	1	0	
Body heigh (cm)	161±7	161±7	0.794
Target of body weight (kg)	57.2±7.8	55.2±11.2	0.577
Body mass index	21.8±2.5	21.1±3.1	0.506
DBP, pre HD (mmHg)	131±20	142±20	0.163
SBP, post HD (mmHg	76±12	90±11	*0.006*
Hand grip strength (kgf*)	28.0±11.0	19.4±14.0	0.075
Upper arm circumference (cm)	23.9±3.9	23.4±3.9	0.715
Triceps skin fold (cm)	0.9 ±0,3	0.9±0.5	0.951
Upper arm muscle circumf. (cm)	20.9±3.2	20.4±3.7	0.700
Waist circumference (cm)	81.7±7.6	83.3 ±9.3	0.611
Hip circumference (cm)	81.0±5.6	84.7±10.0	0.123
Wais to hip ratio	0.99±0.08	1.01±0.06	0.428
Category of hs-CRP levels, pre HD			
> 3.0 mg/dL	3	7	0.121
≤ 3.0 mg/dL	12	8	

*) Kgf: kilogram force

Table 2. Baseline characteristics of subjects in PES and CDA groups (cont'd)

Baseline hemodialysis and dialyzer status	PES group (n=15) Mean±SD	CDA group (n=15) Mean±SD	P-value
Ultrafiltration (liters)	3.1±1.1	3.8±1.0	0.098
Blood flow (ml/mnt)	211±14	195 ±24	0.037
Surface area (m2)	1.30±0.00	1.21±0.10	0.000
Priming volume (mL)	76.9 ±3.4	71.4±5.5	0.003
Duration of session (hours)	4.0±0.3	4.4±0.5	0.013
Duration of HD (mo's)	21.6±18.5	48.8±38.2	0.028

BUN pre HD (mg/dL)	86.2±20.1	83.2±17.4	0.669
BUN post HD (mg/dL)	31.7±12.6	25.2±8.0	0.104
URR (*urea reduction ratio*)	0.64±0.07	0.69±0.07	0.050
KT/V (*delivered*)	1.00±0.22	1.13±0.2	80.173
Albumin, pre HD (g/dL)	4.3±0.3	4.1±0.3	0.045
Albumin, post HD (g/dL)	4.6±0.5	4.1±0.8	0.042
Creatinine, pre HD (mg/dL)	14.6±2.7	14.4±3.8	0.845

Table 3. Baseline characteristics of subjects in PES and CDA groups (cont'd)

Hematological profile	PES group (n=15) Mean±SD	CDA group (n=15) Mean±SD	P-value
Hemoglobin, pre HD (g/dL)	7.0±1.4	7.7±1.1	0.144
Hemoglobin, post HD (g/dL)	7.7±1.6	8.1±1.2	0.440
Hematocrit, pre HD (%)	21.7±4.3	24.5±3.4	0.052
Hematocrit, post HD (%)	23.4±4.8	26.0±4.2	0.130
Leucocytes, pre HD (K/uL)	6.9±1.6	6.9±2.6	0.968
Leucocytes, post HD (K/uL)	6.3±1.5	5.7±1.8	0.386
Eosinophyl, pre HD (K/uL)	0.46±0.27	0.32±0.19	0.111
Eosinophyl, post HD (K/uL)	0.37±0.19	0.26±0.14	0.069
Basophyl, pre HD (K/uL)	0.04 0.02	0.05 0.03	0.369
Basophils, post HD (K/uL)	0.03 0.02	0.03 0.02	0.931
Neutrophils, pre HD (K/uL)	4.18±1.17	4.57±2.02	0.552
Neutrophils, post HD (K/uL)	4.03±1.13	3.94±1.58	0.846
Lymphocyte, pre HD (K/ul)	1.65±0.60	1.35±0.53	0.162
Lymphocyte, post (HD K/uL)	1.44±0.55	1.09±0.28	0.037
Monocyte, pre HD (K/uL)	0.56±0.25	0.57±0.20	0.893
Monocyte, post HD (K/uL)	0.43±0.15	0.44±0.16	0.885

A significant increase of IL-6 post HD levels in comparison to pre HD levels (Z=-2.396, p=0.017), however, similar pre and hs-CRP levels (Z=-1.769, p=0.077) in both groups were found. If changes of IL-6 and hs-CRP levels between both groups before and after HD were compared, a significant increase of IL-6 levels in CDA group compared to PES group (Z=-2.302, p=0.021), however, no significant changes of hs-CRP levels between CDA compared to PES group (Z=-0.270, p=0.806), see table 4.

Table 4. Changes in serum IL-6 and hs-CRP levels before-after HD in PES and CDA groups

Serum levels	PES group (n=15) Median (interquartile)	CDA group (n=15) Median (interquartile)	Total (n=30) Median (interquartile)
IL-6, pre HD (pg/dL)	4.10 (3.38 – 5.90)	11.13 (4.42-14.47)	5.81 (3.61-11.41)
IIL-6, post HD (pg/dL)	5,30 (3.25 – 5.38)	23.11 (6.85-47.12)	6,04 (4.59-29.94)
Change, median	1.20	11.98	
Hs-CRP pre HD (mg/L)	0.73 (0.27 – 1.89)	2.68 (2.06-12.80)	1.97 (0.54-6.58)
Hs-CRP post HD (mg/L)	1.02 (0.43-2.37)	3,58 (2.14-13.40)	2.15 (0.74-7.13)
Change, median	0.29	0.90	

A significant increase of IL-6 per 1000 monocytes post HD levels in comparison to pre HD levels (Z=-4,103, p=0,003) in both groups were found. If changes of IL-6 per 1000 monocytes levels between both groups before and after HD was compared, a significant increase of IL-6 per 1000 monocytes levels in CDA group compared to PES group (Z=-2,883, p=0,003) between CDA compared to PES group, see table 5.

Table 5. Changes in serum IL-6 per 1000 monocytes before-after HD in PES and CDA groups

Serum levels	PES group (n=15) Median (interquartile)	CDA group (n=15) Median (interquartile)	Total (n=30) Median (interquartile)
IL-6/1000 monocyte pre-HD (pg/dL)	9.31 (3.88-16.23)	17.80 (8.66-28.67)	13.35 (6.86-21.84)
IL-6/1000 monocyte post-HD (pg/dL)	14.77 (4.45-17.48)	65.82 (20.75-112.82)	17.86 (12.93-67.72)
Change, median	5.46	48.02	

In order to rule out the effect of intradialytic blood volume changes on changes of serum IL-6 per 1000 monocyte levels and hs-CRP during HD, control for plasma pre-HD albumin/post-HD albumin was performed.

A significant increase of IL-6 per 1000 monocyte post HDX(alb-pre/alb-post HD) (Z=-3.857, p=0.000), however, there was no changes of hs-CRP post-HDX(alb-pre/alb-post HD) (Z=-0.247, p=0.805) levels in both groups were found. If changes of IL-6 per 1000 monocyte post HDX(alb-pre/alb-post HD) and hs-CRP post-HDX(alb-pre/alb-post HD) levels between both groups before and after HD were compared, a significant increase of IL-6 per 1000 monocyte post HDX(alb-pre/alb-post HD) levels in CDA group compared to PES group (Z=-2.717, p=0.006), however, no significant changes of hs-CRP post-HDX(alb-pre/alb-post HD) levels between CDA compared to PES group (Z=-0.62, p=0.967), see table 6.

Table 6. Changes in serum IL-6 per 1000 monocyte and hs-CRP levels after adjustment for pre:post HD plasma albumin ratio, during HD in PES and CDA groups

Serum levels	PES group (n=15) Median (interquartile)	CDA group (n=15) Median (interquartile)	Total (n=30) Median (interquartile)
IL-6/1000 monocyte, pre-HD (pg/dl)	9.31 (3.88-16.23)	17.80 (8.66-28.67)	13.35 (6,86-21,84)
IL-6 per 1000 monocyte post HDX(alb-pre/ alb-post HD)	13.43 (4.10-17.73)	67.65 (18.10-107.44)	17.73 (11.15-73.84)
Change, median	4.12	49.85	
Hs-CRP pre-HD (mg/L)	0.73 (0.27 – 1.89)	2.68 (2.06-12.80)	1.97 (0.54-6.58)
Hs-CRP post-HD X (alb-pre/ alb-post HD) (mg/L)	1.05 (0.40-2.26)	3.67 (2.02-15.43)	2.08 (0.65-7.32)
Change, median	0.32	0.99	

Multivariate ANCOVA analysis was performed in order to control HD factor (KT/V and duration of HD) and pre-HD albumin levels to produce real effect of membrane biocompatibility (PES and CDA) on serum IL-6/1000 monocyte and hs-CRP levels. Plasma albu-

min levels are considered a marker of nutritional status and can be used as prognostic indicator for CV morbidity and mortality (Kaysen, 2000). After logistic transformation ln pre HD IL-6 /1000 monocyte, ln post HD IL-6/1000 monocyte and ln pre HD hs-CRP and ln post HD hs-CRP which were previously non-normal distributed became normally distributed. Using multivariate ANCOVA a significant effect of membrane biocompatibility (F=18.401, p=0.000) on changes of ln IL-6 /1000 monocyte was found. Effect of this membrane biocompatibility was not significant (F=1.937, p=0.176) on changes of ln hs-CRP. It was also found that pre HD plasma albumin levels significantly affect changes of ln IL-6 /1000 monocyte (F=5.610, p=0.026), however, no effect of HD factor (KT/V) and duration of HD (months) on changes of ln IL-6/1000 monocyte and changes of ln hs-CRP was found, see table 7.

Table 7. Multivariate ANCOVA analysis to control for HD factor (KT/V duration of HD) and pre HD albumin on the effect of membrane biocompatibility (PES and CDA) against changes of serum IL-6/1000 monocyte and hs-CRP

Independent variables	Dependent variable	F	P-value
Interventional groups (PESvs. CDA)	Changes of ln (pre-post HD) IL-6/1000 monocyte	18.401	0.000
	Changes of ln (pre-post HD) hs-CRP	1.937	0.176
Pre HD albumin (g/dl)	Changes of ln (pre-post HD) IL-6/1000 monocyte	5.610	0.026
	Changes of ln (pre-post HD) hs-CRP	0.149	0.703
	Changes of ln (pre-post HD) IL-6/1000 monocyte	1.206	0.283
KT/V	Changes of ln (pre-post HD) hs-CRP	2.013	0.168
Duration of HD (month)	Changes of ln (pre-post HD) IL-6/1000 monocyte	3.401	0.077
	Changes of ln (pre-post HD) hs-CRP	1.571	0.222

Analysis for adverse events showed that there were four events of intradialytic hypotension, consisted of two events in polyethersulfone group and two events in cellulose diacetate group.

DISCUSSION

This study showed a significant increase of serum IL-6 after HD (Z=-2,396, p=0,017) in both groups and this increase was more obvious CDA than PES group (Z=-2.02, p=0.21). The increase of IL-6 in both groups were almost as 2,5 times after HD (23 pg/ml) compared to pre HD (10 pg/mL). IL-6 levels was unchanged in PES group (6 pg/ml before HD and 6 pg/ml after HD), however it was increased more than 2.5 times (15 pg/ml before HD and HD 39 pg/mL after HD). The effect of membranes (PES vs. CDA) on serum IL-6 was consistently significant (F=18.401, p<0.001) after multivariate ANCOVA analysis control some confounding variables including HD factors (KT/V and HD duration) and pre HD serum albumin. This results was similar to a report Schouten et al. that cuprammonium a cellulose based membrane induced IL-6 greater than polysulfone synthetic membrane. Memoli et al.[24] also showed that peripheral monocytes of patients with regular HD secreted lower IL-6 after crossed-over HD from cuprophan to synthetically modified cellulose membrane. Monocytes in extracorporeal circulation of HD patients play an important role in producing plasma IL-6. This concept is supported by evidence from in-vitro studies.[19,23]

During contact between blood and membrane, complement pathway is activated and produces neutropenia.[27] This study revealed a reduction of leucocytes and neutrophils after HD in both groups.

Complement system is activated via alternative pathway and C5a activates phagocytic activity of macrophages including monocytes and neutrophils and subsequent adhesion of activated granulocytes in pulmonary circulation.[28,29] Our study showed that HD with PES dialyzer had 0.13 K/ul reduction of monocytes (from 0.56 K/uL up to 0.43 K/uL) during HD and equal reduction was happened in HD with (from 0.57 K/uL to 0.44 K/uL). In this study the increase of IL-6 during HD in CDA group was consistently greater than PES group after adjusted for 1000 pre HD monocytes. Monocytes will infiltrate atherosclerotic lesion and transforms to foam cells. This event will lead the progression of atherosclerosis.[18] The mechanisms of complement activation via contact on artificial membrane depends on physico-chemical properties of the membrane.[30] Consequently, complement activation will lead monocytes to produce pro-inflammatory cytokines such IL-1β, IL-6 and TNF.[18]

During HD, blood water will move across the membrane into dialysate via convective mechanism and leading to hemoconcentration.[31,32] This process depends on ultrafiltration rate during HD. This study has controlled changes in IL-6 levels with degree of hemoconcentration reflected by ration of pre and post plasma albumin levels. Consistently, a significant increase of IL-6/1000 monocyte post-HDX(alb-pre/alb-post HD) in both groups and this increase were more obvious in CDA than PES group.

Interleukin-6 plays important role during inflammatory response. This cytokine induces vascular permeability and initiates acute phase response.[33] This cytokine acts as intercellular communicator through a complex processes.[34] Signal transduction, gene transcription, RNA translation and post translation process transforms precursor of IL-6 to mature cytokine.[12] Interleukin-6 involves in many proliferative, differentiation and maturation process of target cells.[35]

This study showed that although no statistical different (Z=-1.769, p=0.077), there was 7% increase hs-CRP levels during HD (6.53 mg/l pre HD to 6.99 mg/l post HD) was found in both groups. Comparison analysis revealed that changes in serum hs-CRP levels were similar in CDA compared to PES group (Z=-0,270, p=0,806). This serum hs-CRP changes were still consistent after adjusted for plasma pre-albumin:post albumin ratio, and controlled for confounding variables including KT/V, duration of HD and pre HD albumin. This study results were consistent with a previous study about *in-vivo* mechanism of cuprammonium dialyzer biocompatibility a type of unmodified cellulose [25]. In this study HD with synthetic polysulfone (PS) membrane was compared with unmodified cellulose cuprammonium (CU) membrane. It was reported that unmodified cellulose membrane induced greater acute inflammatory response than synthetic membrane, however the increase of CRP levels was just happened 24 hours after contact of the membrane with blood. Meanwhile, CRP levels at 3 hours were similar to baseline CRP levels. Other author reported lower serum CRP levels in HD with polyamide compared with cuprophan dialyzer.[36]

Although cellulose diacetate used in this study is a cellulose based membrane, it is modified cellulose. It is different with cuprophan an unmodified cellulose type membrane. Cuprophan membrane and its analog are simple cellulose membrane called unmodified cellulose.[37] The absence of hydroxyl residue in synthetic membrane will reduce inflammatory response during HD[38]. In this study a relative low response of cellulose diacetate compared to cuprophan in producing CRP by hepatocytes may be explained by modified structure of this cellulose diacetate. CRP is an acute phase beta globulin with molecular weight of 118. 000 dalton. Production of CRP is sharply increased within 24 to 48 hours after acute tissue injury.[39] Limitation of this study is that hs-CRP levels were measured at the end of HD session (5 hours contact with dialyzer) and sharp increase of

CRP levels has not happened yet. Similar results by Schouten et al. (2000) who reported that among HD patients with cuprophan, there were no increase of CRP levels at 3 hours, however, the increase CRP has happened 24 hour after HD.[25] Lack KT/V (KT/V less than 1.8 with HD twice a week) in this study may affect acute phase response which is reflected by lack of increase in CRP levels in both groups. Girndt et al. reported that in HD patients thrice a week with mean KT/V 0,82 a defect of T lymphocyte co-stimulation molecules was observed, however this defect was not found in patients with higher KT/V.[18] HD adequacy is measured by delivery of HD (delivered KT/V). Dialysis Concensus 2002 a guideline by Indonesian Society of Nephrology has recommended ideal target for KT/V is 1.2 for HD three times a week and 1.8 for HD twice a week.[40] It was reported that hs-CRP levels was correlated with IL-6 levels ($r= 0.35$; $p<0.0004$), and both CRP and IL-6 were related to residual kidney function.[41] Lack of protein intake with concurrent chronic inflammation will produce malnutrition and increase the risk of CV morbidity and mortality.[42]

Inflammation process may involve in the pathogenesis of atherosclerosis (Kaysen et al).[43] In non-chronic kidney disease patients PGK there is a close relationship between markers of inflammation and coronary atherosclerosis, cerebrovascular and peripheral.[44] In These patients CRP is associated with worse prognosis such as CV morbidity , ischemic stroke and elderly mortality.[16] It was reported that CRP co-localized with active complement fragments in infracted human myocardium.[45] A similar process is also reported in atherosclerotic blood vessels showing direct proinflammatory role of CRP[27]. Risk of mortality is 100 times higher in HD patients at the age of 40 years compared with normal population.[7] Patients with CRP levels more than 8 – 10 mg/L were prevalent among dialysis patients. High CRP levels may relate to increased production of proinflammatory cytokines such as IL-1, TNF α, in chronic kidney disease patients[8]. It is known that IL-1, TNF α, and endotoxins can induce muscular catabolism via oxidation of branch chain amino acids.[47] The exact mechanism of inflammatory response in chronic kidney disease is not clear There is a relationship between dialysis procedures and reduced kidney function with the increased. In pre-dialytic stage CRP, TNF α,, TNFα, receptors, IL-1 and IL-1 receptors levels are also increased.[48] CRP is best used to monitor the course and severity in acute phase.[49]

Baseline data showed that characteristics of patients in PES and CDA group were not similar. Effect of data imbalance at start should be ruled out using multivariate analysis. Three variables were selected to be included in the model consisted of pre HD albumin, delivered KT/V and duration of HD. In order to control the above three variables multivariate ANCOVA was used. It was found that in addition to biocompatibility of membrane ($F=18.401$, $p=0.000$) plasma pre HD albumin levels ($F=5.610$, $p=0.026$) affect changes of serum IL-6 /1000 monocyte. Relationship between IL-6 and serum albumin in this study is consistent with study by Memoli et al.[26] who reported that serum albumin negatively correlated with IL-6 released by peripheral blood monocyte culture ($r=-0.247$, $p<0.05$). Plasma albumin is nutritional parameter which can be used as prognostic indicator for morbidity and mortality of dialysis patients.[50] This study supports the malnutrition, inflammation and atherosclerosis (MIA) syndrome regarding relationship between malnutrition and inflammation. Central role in this syndrome is played by proinflammatory cytokine (IL6).[42] Patients with kidney disease had reduced nutritional intake since pre-dialytic phase and strongly correlated with reduction of GFR. Reduced nutritional intake is concomitantly occurs with chronic inflammation. Both factors cause malnutrition. Chronic inflammation may inhibit albumin synthesis. Malnutrition and inflammation increase the risk and mortality of CV disease.[42,41]

This study concluded that inflammatory response measured by changes of serum IL-6 per 1000 monocyte during HD is lower in HD using polyethersulfone synthetic membrane in comparison to cellulose based cellulose diacetate membrane. Inflammatory response measured by changes of serum hs-CRP during HD tend to be lower in HD using polyethersulfone synthetic membrane in comparison to cellulose based cellulose diacetate membrane. In addition, plasma pre HD albumin levels affect changes of serum IL-6 during HD. It is suggested that, in HD patients who had inflammation, search for etiologic factors of inflammation is necessary and the use of synthetic membrane may be taken into consideration. Further studies are needed to compare the use of cellulose based dialyzer membrane with synthetic dialyzer membrane with regard to long-term clinical outcomes such as nutritional parameters and cardiovascular events.

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