

*Original Article*

## Dialyzer reuse; Effect on efficiency and biocompatibility

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**Abstract:** Fifteen patients on maintenance haemodialysis were studied before and after reuse of cuprophane hollow-fiber dialysers to assess its biocompatibility and efficiency.

There was a significant increase in hematocrite value and hemoglobin level by the end of dialysis. Also, there was a significant decrease in total leukocyte, (neutrophilic & eosinophilic) and platelet counts with a peak at 15 minutes after the start of dialysis, then there was a gradual increase till the end of dialysis reaching near the predialysis value.

These changes occurred both in the first use and the reuse sessions. The decrease in the neutrophilic count with the reused dialyzer was significantly less compared to first use dialyzer.

The terminal complement complex (TCC) significantly increased and reached its maximum after 15 minutes, then it began to decline till the end of the dialysis. Similarly, these changes were significantly less in the reuse dialyzers. No correlation was found between the changes of the TCC and the decrease in different cellular elements.

There was an increase in plasma bicarbonate and pH by the end of dialysis. Also, hypoxia and hypocapnea occurred shortly after the start of dialysis session with acetate dialysate, but they returned to their predialysis values at the end of both dialysis sessions. This can be attributed to the loss of carbon dioxide into the dialysate with subsequent hypoventilation.

The clearances of urea, creatinine and phosphorus showed insignificant difference between the new and reused dialyzers at zero and 4hr time with significant decrease by the end of dialysis in both

dialysis session. This could be explained by keeping the surface area of the reused dialyzers within the acceptable values (80-100%) of the first use dialyzer.

It can be concluded that reused dialyzers were to some extent more hemocompatible than the first use dialyzers. Complement activation is not the sole factor for the biocompatible reactions during dialysis. Reuse of dialyzers can be a safe procedure by adopting appropriate sterilization, reprocessing and storage techniques and limited number of reuse.

### Introduction

Chronic haemodialysis is one of the major therapeutic modalities for chronic renal failure patients. Many factors determine the costs and it is important to be reduced [1]. The price of dialyzers constitute the major part of dialysis costs. Reuse of dialyzers was instituted in 1964 [1].

Dialysis biocompatibility, can be defined as the sum of specific and non specific interactions between blood and the artificial materials of the dialysis circuit [2].

During contact of blood with the dialysis membranes, a variety of mediator are activated. These may be soluble or cellular [3]. The former include peptides, fatty acids or amines. Among these substances are, complement components (C) fibrinogen, coagulation factors, prostaglandins, thromboxane, leukotriens, kinins and histamine [3].

The cellular factors include, platelets which release thromboxane, neutrophils which lead to release of proteases and toxic oxygen radicals. While

monocyte and lymphocyte activation lead to production of interleukin I and lymphokines respectively [3]. Activation of the complement system occurs by either the classical or the alternative pathway. The classical pathway is initiated with the first component of complement (C1) and the alternative pathway is initiated with the third complement component (C3), with subsequent activation and assembly of the terminal complement components (C6, C7, C8) and multiples of C9 are associated with C5b to form multimolecular membrane attack complex (C5b-9) or the terminal complement complex (TCC) [4].

The C5b-9 complex can react with plasmatc S-protein, a scavenger which keeps the complex in fluid phase. [4].

The aim of this work was to study the effect of reuse of hollow fiber dialyzers on dialysis efficiency and biocompatibility.

## Materials and methods

This study included 15 patients (8 males and 7 females) with end stage renal disease on maintenance haemodialysis (HD) admitted to the Nephrology and Dialysis Unit at Alexandria University Hospital. Their ages ranged between 22-60 year with mean of  $41 \pm 19$  years and the duration of dialysis ranged between 32-88 months with a mean  $60 \pm 28$  months.

We excluded patients with autoimmune diseases, intercurrent infection and those receiving immunosuppressive therapy.

All patients were subjected to full history and thorough clinical examination to define the symptoms and signs of dialyzer reaction as headache, chest pain, dyspnea, vomiting, angioneurotic oedema, rash and muscle cramps.

## Dialysis procedure

In the first use session the dialyzer used was the hollow fiber with cuprophane membrane and  $1\text{m}^2$  surface area.

In the reuse session the dialyzer was reprocessed for one reuse only using ECHO reuse system. Sodium hypochlorite (5.25%) was used for cleaning and dialox solution (peracetic acid 4.5%, acetic acid 6%, and hydrogen peroxide 28%) as a disinfectant and cleaner.

The dialysate was acetate dialysate composed of sodium 134 mEq/l, potassium 2 mEq/l, calcium 4 mEq/l, magnesium 1.5 mEq/l, chloride 105 mEq/l, and acetate 36.6 mEq/l.

Dialysate flow rate was 500 ml/min, the flow of blood pump was at 250 ml/min. The transmembrane pressure (TMP) was adjusted at 100 mmHg and venous pressure ranged from 50-80 mmHg. Water

used for dialysate was purified and treated by sand filter, carbon filter, sofiner, reverse osmosis and bacterial filter. The duration of this dialysis session was four hours, three times weekly.

## Collection of samples

All blood samples were collected at zero time before dialysis, then at 15 minutes and 4 hours from the start of dialysis. The samples were stored at  $-70^\circ\text{C}$ .

## Laboratory studies

1. The following tests were done for all blood samples:
  - a) Hemoglobin (HB) and haematocrit (Ht) [5].
  - b) Platelet count, total and differential leucocytic count by electronic counter. Coulter T540+ [5].
  - c) Arterial blood gas analysis: partial arterial oxygen and carbon dioxide pressure ( $\text{PaO}_2$ ,  $\text{PaCO}_2$ ), plasma bicarbonate ( $\text{HCO}_3$ ) and pH [6].
2. The efficiency of the dialyzers at the first use and reuse sessions was estimated twice; at the start and at the end of dialysis (4 hr). This was achieved by measuring urea, creatinine and phosphate clearances [6,7].
3. The biocompatibility of the dialyzer was measured by estimation of serum level of the end product of complement activation C5b-9 complex using. Enzyme- Linked Immunosorbent Assay (ELISA) technique. The kit was purchased from QUIDEL, San Diego, USA [8]. This kit was used for the quantification of SC5b-9. It was a three-step procedure utilizing: (1) a microassay plate coated with a mouse monoclonal antibody which binds specifically to SC5b-9, (2) Horse radish peroxidase (HRP) conjugated antibodies to antigens of SC5b-9, and (3) a chromogenic substrate [8].

Calculation of the results was done using the standard curve: The absorbance was at 405 value for each SC5b-9 standard (y) and the assigned nanograms of SC5b-9 per ml (ng/ml) value for the standards A, B and C were used to establish the standard curve. The best fit line was drawn on the provided graphic paper. The ng/ml concentration for each diluted sample then was read on the X-axis for each corresponding absorbance 405 value obtained.

## Results

During the first use and the reuse sessions none of the patients had any reaction.

The surface area of the reused dialyzer ranged between 80-100% with a mean of 96% from the intial surface area of the first used dialyzer.

Hemoglobin and hemotacrit values increased significantly during both first use and reuse sessions, reaching its highest value at the end of dialysis (table 1).

**Table 1.** Mean percent change  $\pm$ SD and statistical comparisons of hematocrite (%), hemoglobin (g/dl), platelets ( $\times 10^3$  cell/mm<sup>3</sup>) and terminal complement complex (SC5b-9ng/ml) in the first use and reuse at different periods of dialysis session.

Parameter	0-15 min (A)	15 min-4 hr. (B)	0-4 hr. (C)	F Value
<i>Hematocrite</i>				
First use	4.03 $\pm$ 8.52	11.02 $\pm$ 9.27	15.1 $\pm$ 8.81	5.97* (A,B) (A,C)
Reuse	0.21 $\pm$ 3.65	12.50 $\pm$ 8.80	12.60 $\pm$ 7.72	15.16** (A,B) (A,C)
Student "t"	1.621	0.451	0.831	
Paired "t <sub>1</sub> "	1.832	4.602**	6.641**	
Paired "t <sub>2</sub> "	0.223	5.503**	6.314**	
<i>Haemoglobin</i>				
First use	0.24 $\pm$ 10.23	15.64 $\pm$ 11.90	15.68 $\pm$ 14.82	7.66** (A,B) (A,C)
Reuse	-0.41 $\pm$ 2.99	16.95 $\pm$ 10.18	16.33 $\pm$ 8.80	22.96** (A,B) (A,C)
Student "t"	0.244	0.321	0.152	
Paired "t <sub>1</sub> "	0.091	5.092**	4.097**	
Paired "t <sub>2</sub> "	0.526	6.448**	7.193**	
<i>Platelets</i>				
First use	-16.76 $\pm$ 12.15	22.50 $\pm$ 20.26	-0.02 $\pm$ 6.99	28.78** (A,B) (A,C) (B,C)
Reuse	-6.65 $\pm$ 4.03	11.82 $\pm$ 9.43	4.22 $\pm$ 7.75	23.73** (A,B) (A,C) (B,C)
Student "t"	3.059*	1.854	1.573	
Paired "t <sub>1</sub> "	5.342**	4.301**	0.011	
Paired "t <sub>2</sub> "	6.395**	4.301**	2.108	
<i>Terminal complement complex</i>				
First use	320.67 $\pm$ 342.78	-38.66 $\pm$ 34.52	140.85 $\pm$ 233.88	8.38** (A,B)
Reuse	118.53 $\pm$ 95.54	-23.98 $\pm$ 17.55	70.99 $\pm$ 81.75	14.70** (A,B) (B,C)
Student "t"	2.200*	1.468	1.092	
Paired "t <sub>1</sub> "	3.612**	4.331**	2.334*	
Paired "t <sub>2</sub> "	4.805**	5.291**	3.368**	

t<sub>1</sub> = Paired t of the percent change at different periods in the first use session.  
t<sub>2</sub> = Paired t of the percent change at different periods in the reuse session.  
\* = Significant P value at 5% level.      \*\* = Significant P value at 1% level.

The total leucocytic, oesinophilic, neutrophilic and platelet counts, blood gases (PaO2 and PaCO2), plasma bicarbonate and pH showed an early drop,

followed by rise to reache near thier predialysis level by the end of the dialysis in both sessions (table 1, 2, 3).

**Table 2.** Mean percent change  $\pm$ SD and statistical comparisons of total leuccocytic ( $\times 10^3$  cell/mm<sup>3</sup>) eosinophilic (cell/i-nM3), neutrophilic ( $\times 10^3$  cell/nun<sup>3</sup>) and lymphocytic ( $\times 10^3$  cell/mm<sup>3</sup>) counts in the first use and reuse at different periods of dialysis sessions.

Parameter	0-15 min (A)	15 min-4 hr. (B)	0-4 hr. (C)	F Value
<i>Total leukocytic count</i>				
First use	-56.35 $\pm$ 17.88	210.32 $\pm$ 186.90	10.00 $\pm$ 32.26	23.97** (A,B) (A,C) (B,C)
Reuse	-45.66 $\pm$ 21.74	177.44 $\pm$ 151.33	25.45 $\pm$ 31.43	23.90** (A,B) (A,C) (B,C)
Student "t"	1.485	0.534	1.332	
Paired "t <sub>1</sub> "	12.201**	4.351**	1.205	
Paired "t <sub>2</sub> "	8.114**	4.545**	3.137**	
<i>Eosinophilic count</i>				
First use	-72.88 $\pm$ 27.44	160.99 $\pm$ 182.99	3.34 $\pm$ 45.19	17.65** (A,B) (A,C)
Reuse	-48.43 $\pm$ 45.06	334.66 $\pm$ 283.71	34.50 $\pm$ 72.32	20.83** (A,B) (A,C)
Student "t"	1.795	1.992	1.415	
Paired "t <sub>1</sub> "	10.286**	3.407**	0.286	
Paired "t <sub>2</sub> "	4.162**	4.568**	1.847	

<i>Neutrophil count</i>				
First use	-76.32±11.62	444.15±256.38	-0.17±23.53	53.54** (A,B) (B,C)
Reuse	-65.27±16.05	278.02±156.37	19.82±29.40	56.24** (A,B) (A,C) (B,C)
Student "t"	2.159*	2.142	2.056	
Paired "t <sub>1</sub> "	25.437**	6.709**	0.027	
Paired "t <sub>2</sub> "	15.750**	6.886**	2.610*	
<i>Lymphocytic count</i>				
First use	22.15±94.01	38.44±74.14	27.27±56.33	0.18
Reuse	-10.06±51.59	103.78±149.05	26.24±38.71	5.77* (A,B) (B,C)
Student "t"	1.163	1.520	0.058	
Paired "t <sub>1</sub> "	0.912	2.008	1.874	
Paired "t <sub>2</sub> "	0.755	2.696*	2.625*	

Abbreviations as table 1.

**Table 3.** Mean percent change ± SD and statistical comparison of partial arterial oxygen and carbon dioxide pressures (PaO<sub>2</sub>, PaCO<sub>2</sub> mm Hg), plasma bicarbonate (HCO<sub>3</sub> mEq/L) and pH in patients on maintenance hemodialysis in the first use and reuse at different periods of dialysis sessions.

Parameter	0-15 min (A)	15 min-4 hr. (B)	0-4 hr. (C)	F Value
<i>PaO<sub>2</sub></i>				
First use	-17.71±9.39	17.02±10.14	-4.15±9.84	47.89** (A,B) (A,C) (B,C)
Reuse	-15.82±8.22	20.88±17.38	1.00±12.16	29.33** (A,B) (A,C) (B,C)
Student "t"	0.596	0.741	1.281	
Paired "t <sub>1</sub> "	7.301**	6.494**	1.635	
Paired "t <sub>2</sub> "	7.458**	4.656**	0.311	
<i>PaCO<sub>2</sub></i>				
First use	-28.91±19.57	47.85±45.62	-2.15±15.62	25.22** (A,B) (A,C) (B,C)
Reuse	-13.43±13.55	31.71±24.31	12.28±18.66	20.54** (A,B) (A,C) (B,C)
Student "t"	2.521*	1.243	2.315*	
Paired "t <sub>1</sub> "	5.721**	4.063**	0.532	
Paired "t <sub>2</sub> "	3.834**	5.056**	2.545*	
<i>Plasma HCO<sub>3</sub></i>				
First use	-6.88±11.28	36.78±21.45	25.77±14.12	29.49** (A,B) (A,C)
Reuse	-2.28±5.71	31.58±14.14	28.33±14.03	36.68** (A,B) (A,C)
Student "t"	1.444	0.781	0.525	
Paired "t <sub>1</sub> "	2.362*	6.465**	7.061**	
Paired "t <sub>2</sub> "	1.541	8.561**	7.842**	
<i>pH</i>				
First use	-0.12±0.67	2.04±0.273	1.92±0.95	34.71** (A,B) (A,C)
Reuse	-0.29±0.75	2.19±0.61	1.89±0.82	50.93** (A,B) (A,C)
Student "t"	0.676	0.621	0.080	
Paired "t <sub>1</sub> "	0.678	10.711**	7.792**	
Paired "t <sub>2</sub> "	1.491	13.832**	8.914**	

Abbreviations as table 1.

There was a significant increase in the TCC (SC5b-9) level at 15 minutes then it declined till the end of dialysis, although it remained higher than the predialysis level. This occurred both at the first use and reuse sessions (table 1).

The decrease in the neutrophil and platelet counts and the increase in S5b-9 level were significantly less in the reuse session than the first use session (table 1,2). Urea, creatinine and phosphorus clearance decreased significantly by the end of dialysis (4 hrs). This

decrease was insignificantly different comparing the first use and reused dialyzers (table 4).

There was a significant positive correlation between the % changes of the surface area after reuse and urea and creatinine clearance at zero time ( $r = 0.686$ ,  $0.700$  respectively) and at 4 hr time with creatinine clearance only ( $r = 0.584$ ).

No correlation was found between the % change of TCC (Sc5b-9) and the neutrophilic count at both the first use and the reuse session at 0-15 min and 15

min – 4 hr times. (r = -0.232, 0.100, -0.331, -0.054 respectively).

**Table 4.** Mean ±SD and statistical comparisons of urea, creatinine and phosphorous clearances (nil/min) at the beginning and the end of the first use and reuse sessions.

Parameter	0 min	4 hr.	0 min-4 hr. % change	Paired "t"
<i>Urea Clearance</i>				
First use	128.89±16.32	107.53±18.22	-15.86±13.56	4.531**
Reuse	115.53±12.23	96.00±16.61	-16.73±11.91	5.442**
Student "t"	2.512*	1.810	0.191	
<i>Creatinine clearance</i>				
First use	134.13±19.25	119.80±14.16	-10.03±8.39	4.622**
Reuse	124.80±16.60	111.27±19.24	-10.89±9.26	4.552**
Student "t"	1.425	1.385	0.271	
<i>Phosphorous clearance</i>				
First use	114.78±25.32	103.80±14.86	-6.54±17.92	1.411
Reuse	104.20±20.46	95.13±32.15	-8.08±31.87	0.987
Student "t"	1.261	0.951	0.165	

Abbreviations as table 1.

**Discussion**

This study showed that the TCC orC (SC5b-9) as one of the parameters of biocompatibility was significantly increased early in both dialysis session which was less in the reuse than the first use session denoting that reused dialyzers were more biocompatible, although still activate the complement cascade to a certain extent. These results agree with the results of Deppisch et al [8] who first describe the use of TCC as sensitive index of bioincompatibility in haemodialyzed patients. The other complement (C) components specially C3a and C5a were also found by many authors to be increased during dialysis using unsubstituted cellulose dialyzers than the synthetic modified cellulose or in the reused dialyzers [9-12]. The increase in complement components during dialysis reflect the balance between its activation and clearance. Also, the subsequent decline could be related to deposition of C fragments on the activating sites of the dialyzer membrane surface or loss in the dialysate [9-12]. Both the SC5b-9 and peripheral leukocyte are not expected to penetrate the dialyzer membrane, so measurement of TCC may be an index of biocompatibility, complementary to and independent of the C-anaphylatoxins [8]. The complement system stimulates nucleated cells with the release of different cytokines [3,13]. Dialysis associated leukopenia and thrombocytopenia were studied as parameters of bioincompatibility. Both occurred in the first use and the reuse sessions but was less with the reused dialyzer than with the

first use dialyzer, this also denote that reused dialyzers are more biocompatible than the new one. Hemodialysis induced neutropenia was also observed and reported by many authors [13-18]. Neutropenia is associated with increased expression of cell surface adhesion molecules that was supposed to be stimulated by complement activation [19]. Himmelfarb et al, [19] concluded that MAC-1 expression induce changes in granulocyte cell surface with subsequent the development of granulocytopenia with their adherence to the dialysis membrane and sequestration in the pulmonary capillaries, but it is not sufficient to maintain it. The subsequent reversal of the neutropenia was secondary to the decrease in the CAM-1 expression with down regulation of another adhesion receptors of the selectin family (LAM-1) with their shedding from their attaching surface receptors to return back to the circulation. The absence of correlation between TCC changes and changes in blood count, may suggest that complement was not the sole mediator of neutropenia and changes in other cellular factors. Other factors such as cytokines, chemotactic factors and lipopoly-saccharides may be important [20,21]. Studies done on the effect of reprocessing to improve dialysis induced neutropenia yielded controversial results and this can be explained by the different reuse methods and the type of membranes studied [9,10,12,18]. The beneficial effect of reuse had been attributed to the protective coating of the surface of dialyzer membrane during its first use, particularly the

fixation of C3b on cuprophane, which could block complement activating sites [9,12].

Heparin induced thrombocytopenia (MT) had been reported in 5% of (22) patients with endothelial cell injury.

The increase in Hb and Ht values by the end of dialysis could be attributed to the relative hemoconcentration due to ultrafiltration. This was supported by the finding of negative correlation at end of dialysis between changes of atrial natriuretic peptide (ANTI) and blood volume and Ht [23].

The occurrence of hypoxemia and hypocapnea early in dialysis was the subject of many investigations, [14,24,25].

Hypoxemia and the early decrease of plasma  $\text{HCO}_3$  and pH were attributed to many factors including alveolar hypoventilation following carbon dioxide losses into the dialysate ( $\text{CO}_2$  unloading), intrapulmonary leukostasis, changes in the respiratory quotient during acetate metabolism and direct effect of acetate on the central respiratory center. The subsequent rise of these parameters was related to the correction of acidosis by acetate buffer in the dialysate [24,25].

The efficiency of the reused did not differ from that of the first use dialyzer and the decrease of efficiency by the end of dialysis was the same in both dialysis sessions. This could be explained by keeping the surface area of the reused dialyzer which was within the acceptable value (80-100%) of surface area of the first use dialyzer [26].

In this study none of the patients had symptoms or signs of dialyzer reactions neither in the first use nor in the reuse sessions. This could be partly attributed to proper rinse of the fresh hollow fiber dialyzer with saline before dialysis. This process could wash out any traces of the steriliser used which was the ethylene dioxide (ETO). It was claimed that it can cause type I hypersensitivity reaction and anaphylaxis [27-29].

Controversial results were shown by different studies due to the use of different techniques of sterilization and / or cleaning of the dialysers during reuse process [10, 28-31].

Septicemia and endotoxemia had been also reported with reused dialysis [1,11,21].

Underdialysis had been reported with the reuse dialyzer, but could be due to many causes including improper technique of reuse, errors in setting blood flow, blood access recirculation and short dialysis duration [32,33].

We can conclude that following appropriate procedures, implementation of quality assurance systems and close monitoring of all procedures, dialyser reuse is safe, ensures effective therapy and provides economic benefit.

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