BANTAO Journal 2009; 7 (2): 28-32

BJ
BANTAO Journal

Original article

The Possible Effect of the Dialyzer Membrane on Outcome of Patients with Acute Kidney Injury

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Abstract

Background. Laboratory experiments showed that synthetic membranes tended to cause less activation of complement and mononuclear cells, and clinical studies were set up to evaluate whether membrane choice affected outcomes in acute kidney injury (AKI). The aim of this prospective, randomized study was to asses the importance of dialysis membranes with different degrees of biocompatibility and permeability on the survival and recovery of renal function in AKI patients requiring hemodialysis (HD).
Methods. A total of 297 AKI patients were included in the study and followed until death or discharge from the hospital and/or HD. Four types of dialysis membranes were used with different characteristics of biocompatibility and permeability: low-flux modified cellulose (LF-MC; cellulose acetate, cellulose diacetate, hemophan), high-flux modified cellulose (HF-MC; cellulose diacetate, cellulose triacetate), low-flux synthetic (LF-S; polysulfone) and high-flux synthetic (HF-S; polysulfone, polyacrylnitrile, polymethyl methacrylate). Severity of illness was determined at initiation of HD treatment using the score on the Acute Physiology, Age, and Chronic Health Evaluation II. Outcome measures included survival, cause of death, recovery of renal function, the number of HD sessions, and the number of days from the first HD treatment to death or the recovery of renal function. Delivered urea dialysis dose (Kt/V) was calculated.
Results. In the LF (MC or S) membrane group, causes of AKI were medical (58.4%), surgical (39.4%) or obstetric (2.2%), and all patients treated with HF (MC or S) membranes developed AKI after open heart surgery. There were no significant differences between MC and S subgroups in each LF or HF HD membrane group in the etiology of AKI. There was no difference between the four membrane groups in survival (LF-MC 59.3% *vs*. LF-S 61%, and HF-MC 55.6% *vs*. HF-S 53.3%) or in the recovery of renal function (LF-MC 47.8% *vs*. LFS 48.6%, and HF-MC 90% *vs*. HF-S 100%). The main cause of death in the AKI patients treated with LF MC or S membranes was multi organ damage syndrome (MODS), followed by sepsis. The most of the patients who developed AKI after open heart surgery and were dialyzed with HF MC or S membranes died because of heart failure, and the second cause of death was MODS. There was no difference in MC and S membrane (LF or HF) treated AKI patients in number of HD sessions, duration of HD treatments, and hospitalization.
Conclusion. The use of S (LF or HF) dialysis membranes, as compared with MC (LF or HF) membranes, had not significant influence on the survival and recovery of renal function in patients with AKI requiring HD.

Keywords: acute kidney injury; biocompatibility; bio-incompatibility; dialyzer membrane; outcome

Introduction

Despite many medical and technical advances in patient management, the prognosis of acute kidney injury (AKI) requiring dialysis has not improved significantly during the last decades, with an overall mortality rate exceeding 50% [1,2]. This high mortality rate may be ascribed to increased number of concurrent conditions (multi organ damage syndrome – MODS) and changes in the causes of AKI [3,4]. Laboratory experiments showed that synthetic membranes tended to cause less activation of complement and mononuclear cells, and clinical studies were set up to evaluate whether membrane choice affected outcomes in AKI. Initial reports suggested improved patient outcomes in AKI when non-cuprophan dialyzer membranes were used [5,6]. However, over time these positive observations have not been substantiated [7,8].
The aim of this prospective, randomized study was to asses the importance of dialysis membranes with different degrees of biocompatibility and permeability on the survival and recovery of renal function in AKI patients requiring hemodialysis (HD).

Patients and Methods

All adult patients who were hospitalized at Sisters of Mercy University Hospital (Zagreb, Croatia) between February 1991 and December 1998, and at Magdalena Special Hospital for Cardiovascular Surgery and Cardi-

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ology (Krapinske Toplice, Croatia) between April 1998 and December 2003, and required HD for AKI were eligible for enrolment in this study. After decision has been made to initiate HD, the eligible patients were randomized to one of the four types of dialysis membranes which were than used for all subsequent HD sessions.
All patients received the intensive treatment strategy underwent intermittent HD seven times per week (daily).
A total of 297 patients were included and followed until death or discharge from the hospital and/or HD. Four types of dialysis membranes were used with different characteristics of biocompatibility and permeability: low-flux modified cellulose (LF-MC; cellulose acetate, cellulose diacetate, hemophan), high-flux modified cellulose (HF-MC; cellulose diacetate, cellulose triacetate), low-flux synthetic (LF-S; polysulfone) and high-flux synthetic (HF-S; polysulfone, polyacrylnitrile, polymethyl methacrylate). All HD treatments were performed with a volumetric-control monitors that allowed precise ultrafiltration (UF). Dialysis water was obtained from reverse osmosis, and bicarbonate-based dialysate was used in all patients. Dialysate flow rate was between 500 and 700 ml/min, and blood flow rate was maintained between 200 and 350 ml/min. Dialysate concentrations of sodium, potassium, calcium and glucose, UF, and anticoagulant dose were adapted at each HD session by a nephrologist according to patient needs.
In all treatment groups intermittent HD was prescribed to provide a single-pool Kt/V_{urea} (a dimensionless index of the dialysis dose in which K is the urea clearance of the dialyzer, t is the duration of dialysis, and V is the volume of distribution of urea) of >1.0 per session, at least. Delivered urea Kt/V was calculated from pre- and post-dialysis blood urea nitrogen concentration (9).
Severity of illness was determined at initiation of HD treatment using the score on the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) (10). Outcome measures included survival, cause of death, recovery of renal function, the number of HD sessions, and the number of days from the first HD treatment to death or the recovery of renal function.
Recovery of kidney function was defined on the basis of creatinine clearance (CrCl), measured with the use of 6-hour timed urine collections when the urine flow increased to more than 30 ml/hour or when there was a spontaneous fall in the serum creatinine level. Intermittent HD was discontinued if the CrCl was >20 ml/min/ $1.73m^2$. Recovery of kidney function was considered to be complete if the serum creatinine level was no more than 44 µmol/L above the baseline value or partial if the level remained at more than 44 µmol/L above the baseline value but the patient was not HD-dependent.
Data evaluation was performed by statistical tests (chi-square test, analysis of variance, and t-test). P values less than 0.05 were considered to indicate statistical significance.

Results

The study included 297 AKI patients, 113 in LF-MC membrane group, 36 in HF-MC membrane group, 118 in LF-S membrane group, and 30 in HF-S membrane group. Demographic and clinical characteristics of the patients are shown in Table 1. There were no significant differences between two main groups (MC and S membrane treated patients) in terms of sex, and presence of anuria or oliguria, but the AKI patients treated with HF-MC or HF-S membranes were significantly older (P< 0.001), had significantly more often dysfunction of three or more organ systems (P<0.001), and had significantly higher APACHE II score (P<0.001). There were no significant differences between subgroups (LF-MC or LF-S, and HF-MC or HF-S HD membranes) in demographic data, severity of illness, prevalence of anuria or oliguria, and need for organ support.

Table 1. Demographic and Clinical Characteristics of the AKI Patients at the Time of Initiation of Hemodialysis

		LF-MC (N=113)	**LF-S (N=118)**	**HF-MC (N=36)**	**HF-S (N=30)**
F		63 (55.8%)	67 (56.8%)	17 (47.2%)	14 (46.7%)
M		50 (44.2%)	51 (43.2%)	19 (52.8%)	16 (53.3%)
Age (yr)		51.9±16.3	53.1±18.4	60.5±7.3*	61.9±6.2*
MODS	≥2	83 (73.5%)	82 (69.5%)	9 (25.0%)*	6 (20.0%)*
	≥3	30 (26.5%)	36 (30.5%)	27 (75.0%)	24 (80.0%)
Anuria		51 (45.1%)	46 (39.0%)	15 (41.6%)	13 (43.3%)
Oliguria		62 (54.9%)	72 (61.0%)	21 (58.3%)	17 (56.7%)
APACHE II		28.4± 7.6	28.1±10.3	35.3± 6.9*	36.2± 8.7*

Abbreviations: low-flux modified cellulose, LF-MC; low-flux synthetic, LF-S; high-flux modified cellulose, HF-MC; high-flux synthetic, HF-S
*P < 0.001 *vs.* LF (MC or S) membranes

In the LF (MC or S) membrane group, causes of AKI were medical (58.4%), surgical (39.4%) or obstetric (2.2%), and all patients treated with HF (MC or S) membranes developed AKI after open heart surgery.
There were no significant differences between MC and S subgroups in each LF or HF HD membrane group in the etiology of AKI (Table 2).

Table 2. Etiology of AKI

	Modified cellulose	Synthetic
Dialyser membrane (low-flux)		
	(N=113)	(N=118)
Medical		
Toxic	23 (20.4%)	28 (23.7%)
Sepsis	12 (10.6%)	16 (13.6%)
Miscellaneous	35 (31.0%)	21 (17.8%)
Surgical		
Trauma	14 (12.4%)	19 (16.1%)
General surgary	26 (23.0%)	32 (27.1%)
Obstetric	3 (2.7%)	2 (1.7%)
Dialyser membrane (high-flux)	**Modified cellulose**	**Synthetic**
	(N=36)	(N=30)
Open heart surgery		
Ischemia	18 (50.0%)	14 (46.7%)
Toxic	8 (22.2%)	7 (23.3%)
Sepsis	10 (27.8%)	9 (30.0%)

Although there was no significant differences in delivered dialysis dose per treatment and per week between MC and S membranes, both in the groups of AKI patients treated with LF or HF dialyzers, AKI patients treated with HF-MS or HF-S dialyzers received significantly higher Kt/V in comparison with patients who were dialyzed with LF-MS or LF-S dialyzers (Table 3).

There was no difference between the four membrane groups in survival (LF-MC 59.3% *vs.* LF-S 61%, and HF-MC 55.6% *vs.* HF-S 53.3%) or in the recovery of renal function (LF-MC 47.8% *vs.* LF-S 48.6%, and HF-MC 90% *vs.* HF-S 100%). The main cause of death in the AKI patients treated with LF-MC or S membranes was MODS (44.6%), followed by sepsis (21.7%). The most of the patients who developed AKI after open heart surgery and were dialyzed with HF-MC or S membranes died because of heart failure (50%), and the second cause of death was MODS (30%). There was no difference in LF-MC and LF-S or HF-MC and HF-S membranes treated AKI patients in number of HD sessions (LF-MC 7.1±5.0, LF-S 6.3±4.8, NS; HF-MC 13.6±6.9, HF-S 12.8±9.1, NS), overall duration of treatment by HD (LF-MC 20.9±12.4, LF-S 19.8±14.2 days, NS; HF-MC 29.3±19, HF-S 31.1±20.1 days, NS), and length of hospitalization (LF-MC 30.2±14.3, LF-S 29.1±15.4 days, NS; HF-MC 37.8±18, HF-S 38.6±22.8 days, NS). A total 53 of 139 patients (38.1%) in the LF group (LF-MC 38.8% and LF-S 37.5%), and 23 of 36 patients (63.9%) in the HF group (HF-MC 65.0% and HF-S 62.5%), had complete recovery of kidney function by day 28, and in the LF group (LF-MC 9.0% and LF-S 11.1%), and in the HF group (HF-MC 25.0% and HF-S 37.5%) patients had partial recovery. There were no significant differences in the complete or partial recovery of kidney function between LF-MC and LF-S, or HF-MC and HF-S groups.

Table 3. Delivered Dialysis Dose in AKI Patients Treated with Four Different Types of Dialysis Membranes

	Low – flux membranes		**High – flux membranes**	
	MC (N=113)	**S (N=118)**	**MC (N=36)**	**S (N=30)**
dKt/V	1.05±0.08	1.06±0.11	1.31±0.12*	1.33±0.10*
wKt/V	4.92±0.31	5.02±0.44	9.23±0.79*	9.31±0.71*

*P<0.001 *vs.* LF (MC or S) membranes (d or wKt/V)

Discussion

Among the dialysis membranes, unsubstituted cellulosic cuprophane obviously imposes the most important complement and leukocyte activation leading to neutrophilic infiltration into the kidney and other tissues and prolonged AKI [11]. Remaining cellulosic membranes, and especially the synthetic membranes, induce a less pronounced or no response [12]. The choice of dialyzer membrane may potentially affect not only solute clearances but also blood-dialyzer interactions. Although on one hand alteration of the dialyzer surface or pore size to increase inflammatory mediator loss may potentially be beneficial for patients with AKI, dialyzer membrane interactions, which precipitate intradialytic hypotension, may worsen AKI. In studies by Hakim *et al.* [5] and Schiffl *et al.* [6], the use of cuprophane membrane dialyzers had a negative impact on the survival rate of AKI patients, the occurrence of sepsis, the length of oliguria, and the rate of recovery compared with the use of S membrane dialyzers. In one multicenter prospective study, 153 patients with AKI who required dialysis were randomized to therapy with a bioincompatible or biocompatible HD membrane [13]. At equivalent disease severity the patients treated with biocompatible in comparison with bioincompatible membranes had a higher rate of survival (57% vs. 46%), and an improvement in recovery of renal function (64% vs. 43%). Among nonoliguric patients, a more rapid recovery were observed for those dialyzed with biocompatible membranes as evidenced by fewer mean dialysis treatments before recovery (4 vs. 15 HD sessions). Furthermore, 70% of nonoliguric patients became oliguric on bioincompatible membranes, and only 44% of patients dialyzed on biocompatible membranes [13].

However, there are prospective, randomized or multicentar studies on the epidemiology and treatment of AKI, where a beneficial effect of S over MS membranes was not observed [14,15]. Jörres *et al.* [14] performed a prospective randomized multicentre trial in patients with dialysis-dependent AKI treated with two different types of LF membrane. Eighty patients with AKI were randomly assigned bioincompatible cuprophan (n=90) or polymethylmethacrylate (n=90) membranes. At the start of dialysis, the groups did not differ significantly in age, sex, severity of illness (as calculated by APACHE II scores), prevalence of oliguria, or biochemical measures of AKI. There were no differences in outcome for patients with dialysis-dependent AKI between those treated with cuprophan membranes and those treated with polymethyl-methacrylate membranes [14]. Gastaldello *et al.* [15] performed a prospective, randomized, single centre study on 159 AKI patients requiring HD. Patients were stratified according to age, gender, and APACHE II score and then randomized in chronological order to one of three dialysis membranes: LF polysulfone, HF polysulfone and meltspun cellulose diacetate. Etiologies of AKI and the prevalence of oliguria were similarly distributed among the three groups. Survival was significantly influenced only by the severity of the disease state (APACHE III score, $P<0.0001$), but not by the nature of the dialysis membrane ($P=0.57$) or the presence of oliguria ($P=0.24$). Among patients with AKI requiring HD survival and recovery time were not significantly influenced by the use of either meltspun cellulose diacetate or the more biocompatible HF or LF polysulfone [15].

Because of the differences reported in original trails (including our study), several meta-analyses have been conducted [16-18]. These showed that although there was a possible patient survival and renal recovery advantage when synthetic membranes were compared with cuprophane membranes, there was no difference between synthetic and altered cellulosic membranes. In a 2005 meta-analysis from the Cochrane database, 9 studies with a total of over 1000 patients were reviewed [19]. The relative risk for mortality and recovery of renal function was similar with both biocompatible and bioincompatible membranes (the same with HF and LF membranes). Possible explanations for the discrepant results with the membranes of different biocompatibility and flux, are that the effect of complement-activating membranes on outcomes is not large and/or requires a long period of follow-up to be detected, or that other prognostic determinants, such as comorbidity or physician and nursing skills, are more significant factors.

Dialyzer membrane flux is currently defined according to β_2-microglobulin (a middle molecule) clearance. Traditionally, HF membranes were synthetic, and caused less inflammatory reaction in the extracorporeal circuit, compared with standard LF cuprophan bioincompatible dialyzers. Ponikvar *et al.* [20] treated 72 patients in intensive care units of the University Medical Center Ljubljana, randomized according to the dialyzer used throughout the duration of HD treatment. There were 38 patients in the LF and 34 patients in the HF group. Both groups were balanced in terms of sex, age, APACHE II score, oliguria before dialysis, cause of AKI, innotropic support, mechanical ventilation, and the number of failing organs. The patients' survival rate was 18.7% in the LF group and 20.6% in the HF group. Ten patients (26.3 %) recovered their renal function in the LF group and 8 (23.5 %) in the HF group. Hemodialysis treatment lasted 11.2 days in the LF and 10.7 days in the HF group. An analysis of subgroups with a lower mortality rate (subgroup of patients without oliguria and subgroup of patients with less than 4 failed organ systems) did not show significant differences between the LF and HF groups in terms of survival rate, recovery of renal function, and duration of HD treatment [20]. The number of failing organs seems to be the most important single factor determining the survival of patients with AKI as a part of MODS.

The present prospective, randomized study investigated the role of the dialyzer membrane in the outcome of AKI in 297 patients. To investigate the possible roles of biocompatibility and permeability of the dialyzer membrane, we compared S membranes with either LF or HF characteristics to a LF or HF MC membranes which were also less biocompatible. The nature of the membranes used had no significant influence on survival, recovery of renal function, on the required number of HD sessions, or on the hospitalization. The MC (LF or HF) membranes were just as effective as S (LF or HF) membranes in the treatment of AKI patients. Whether this is directly consequent upon the choice of dialyzer membrane, or related to improvements in dialysate water quality, dialysis doses, or changes in other clinical practices remains to be determined.

HF membranes contain large pores that allow for enhanced permeability of putative toxins, but it could also allow the back transport from dialysate to patient blood of potentially harmful water-borne molecules. Therefore, the ultra-pure dialysate should be a goal when using HF membranes to utilize their positive characteristics and to minimize their potential risks.

Conclusion

The use of S (LF or HF) dialysis membranes, as compared with MC (LF or HF) membranes, had not significant influence on the survival and recovery of renal function in patients with AKI requiring HD. However, given that the effect of biocompatible dialysis membranes is consistently beneficial and that differences in cost are no longer so important, we favor the routine use of biocompatible dialysis membranes in this setting. If the ultra-pure dialysate is available, we suggest the use of HF biocompatible dialysis membranes in the AKI setting, but if the water system is not of high quality, LF biocompatible dialysis membranes should be used.

Conflict of interest statement. None declared.

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