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CLINICAL STUDY

The Effect of the Type of Membrane on Intradialytic Complications and Mortality in Crush Syndrome

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Aims. There are not enough data about the type of the membrane that should be used in acute intermittent hemodialysis (IHD) in patients with crush syndrome where intradialytic complication rate is high. The effects of dialyzers on outcome have been investigated in this study. **Methods.** Patients who required IHD due to crush syndrome after a big earthquake that struck Marmara in 1999 have been studied. Hemodynamic and biochemical analyses at the time of admission were examined. The patients were divided into three groups according to the type of dialyzers (viz., hemophan, polysulfone, and combined). **Results.** Forty-five patients were included in the study (mean age: 33.9 ± 13.3 years, mean HD session per patient: 8.8 ± 6.1). In all, 408 dialyzers were used during IHD therapy (21% hemophan). The types of dialyzers used were hemophan (8 patients), polysulfone (18 patients), and the combination of the two (19 patients). The demographic and biochemical parameters related to crush syndrome were not different statistically. All sessions were anticoagulant-free. Hypotension and coagulation of sets were the main intradialytic complications. Five (11%) patients died, but there was no correlation between mortality rates and the type of the dialyzer used.

Serum albumin, blood pressure, and thrombocyte counts were found to be related to mortality. **Conclusion.** No effect of the type of dialysis membrane on outcome was detected in patients with crush syndrome. Other potential factors, which may responsible for the complications and mortality, should be investigated.

Keywords dialyzer, crush syndrome, acute renal failure, outcome

INTRODUCTION

Acute renal failure is a syndrome characterized by retention of nitrogenous products due to loss of renal function within days, even within hours.^[1] One of the causes of acute renal failure is rhabdomyolysis, which is characterized by destruction of skeletal muscle. Acute renal failure can be prevented in patients with rhabdomyolysis caused by crush syndrome, if treated early with vigorous fluid replacement therapies.^[2] Dialysis is life-saving in case severe renal failure develops. Though new studies have been performed, it has been shown that myoglobin can be cleared with neither peritoneal dialysis nor hemofilters with high permeability.^[3]

It is thought that free oxygen radicals on the membrane activate complement system and neutrophils within

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the blood running from the dialyzer, if pure cellulose membranes are used during hemodialysis.^[4,5] Humoral systems like kallikrein-kinin pathway and coagulation systems can also be activated during dialysis.^[6] Because biocompatible membranes cause the least inflammatory response and carry completely “inert” surface, the use of biocompatible membranes decreases complement activation and the number of dialysis sessions as well.^[4,5,7] Hemophan, which is a cellulosynthetic membrane, activates complement system and causes neutropenia more than synthetic polysulfone membrane.^[8,9] There are insufficient data about the type of the membrane, which should be used in acute intermittent hemodialysis (IHD) in patients with crush syndrome, where intradialytic complication rate is high, anticoagulation during dialysis is contraindicated, and in fact transfusion of blood and its products is frequently necessary.

The role of IHD treatment in patients with acute renal failure due to crush syndrome and the effects of dialyzers on outcome have been investigated in this study.

MATERIALS AND METHODS

Seventy-four patients (35 male, 39 female, mean age = 31.8 ± 13.8 years) followed with nephrologic problems due to crush syndrome after the big earthquake that struck Marmara on June 17th, 1999, have been studied in this retrospective study.

For the purpose of this analysis, at least one of the following criteria were used: the presence of crush injury and urine output <400 mL/day and/or BUN >40 mg/dL, serum creatinine >2.0 mg/dL, uric acid >8.0 mg/dL, potassium >6.0 mEq/L, phosphorus >8.0 mg/dL, bicarbonate <15 mEq/L, and/or serum total calcium <8.0 mg/dL.

All data concerning the patients' demographics, physical and laboratory findings, and treatment modalities and outcomes were collected retrospectively from the hospital files, and the patients who required dialysis therapy were determined. The modality of dialysis was determined, and the patients who were treated with IHD without any anticoagulation constituted the study population. Dialysate composition was 140 mmol/L sodium, 3.5 mmol/L calcium, and free of potassium and glucose. Dialysate flow rate was 500 mL/min; however, blood flows and ultrafiltration volumes were not standardized but were instead dynamically adjusted according to patients' status.

The blood pressure, daily urine output, temperature, serum creatinine, uric acid, K, Ca, P, CPK, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), albumin, BUN, hematocrit levels, and leukocyte and thrombocyte counts at the time of admission were examined. Biochemical studies were

carried out with the autoanalyzer with DAX-72 choice, and hematological measurements were performed with Technicon H-2 device. All surgical procedures including especially the fasciotomies were recorded in a detailed fashion.

Indications of dialysis therapy were defined as azotemia, hypervolemia, and hyperkalemia. Hemodialysis access was provided by catheters inserted percutaneously to central veins. Regional or no heparinization protocols were used intermittently for 3–4 hours. Hemodialysis was performed by Baxter SPS550 or Fresenius 4008/B.

The total number of hemodialysis sessions and duration of IHD were calculated. The number and localization of the hemodialysis accesses as well as the type and number of the dialyzers used were determined. Intradialytic complications like hypotension (systolic blood pressure less than 80 mmHg) and coagulation problems and the transfusion of blood and blood products were recorded. The mortality rate was then calculated.

The patients were divided into three groups according to the type of dialyzer used: the hemophan group was dialyzed with only semisynthetic and the polysulfone group with only polysulfone dialyzers. The combined group was dialyzed both with semisynthetic and polysulfone membranes. The choice of dialyzers was not by preference of the treating physicians; during the disaster period, it was determined by the flow of local and international aids. All of the groups were compared according to their demographic and clinical parameters, laboratory values, morbidity, and mortality of hemodialysis treatment.

The statistical analysis was carried out with Statistical Package for Social Sciences for Windows ver. 10.0 (SPSS Inc, Chicago, Illinois, USA). Numerical variables were given as mean \pm standard deviation. Two groups were compared with paired Student's *t*-test or Mann Whitney *U* tests when necessary. Chi-square test with Yates correction and Fisher's exact test were used for 2×2 contingency tables when appropriate for non-numerical data. Correlations between numerical parameters were analyzed with Spearman's rho correlation test. Groups were compared with Student's *t*-test or analysis of variance (ANOVA) as necessary. Comparisons in the more than two groups were made by Kruskal Wallis-H analysis of variance when the distribution was abnormal. Tukey HSD was used for post-hoc comparisons. *p* values less than 0.05 were accepted as significant.

RESULTS

In all, 52 of 74 (70%) patients involved in the study received renal replacement therapy. Intermittent hemodialysis was performed in 45 (87%) patients, while

continuous renal replacement therapy was used in 5 (10%) patients.

Twenty-one (47%) of 45 patients were male, while 24 (53%) were female. The mean age of patients was 33.9 ± 13.3 (16–62) years. The mean duration under the rubble was 8.8 ± 3.8 (2.5–20) hours. The demographic characteristics of the patients are summarized in Table 1. It was realized that a majority of the patients (22 patients, 49%) had been referred from Golcuk, a city about 130 km from the epicenter of the earthquake.

The mean systolic and diastolic blood pressures were 140.9 ± 30.6 and 83.6 ± 17.4 mmHg, respectively. Twenty-four-hour urine sample was collected in 42 (93%) patients, and the mean amount was 664 ± 1711 ml. The mean body temperature of 23 (51%) patients was recorded as 37.9 ± 0.8 (36.8–40)°C. The laboratory data of the patients on admission are presented in Table 1.

There was no statistically significant difference between the age and gender of the groups when demographic

parameters were compared ($p > 0.05$). The time under the rubble, serum BUN, K, Ca, P, LDH, AST, ALT, albumin, leukocyte and hematocrit levels, temperature, systolic and diastolic blood pressure levels, catheterization numbers, and daily urine outputs of the patients in all groups were not different significantly (see Table 1). Thrombocyte counts in the polysulfone group and the combined group was different (see Table 1). The time under the rubble was longer in the hemophan group, though not statistically significant. All of the patients in polysulfone group were referred from cities other than Istanbul.

Fasciotomies had to be performed in one extremity in 25 (56%) patients; two extremities in 8 (18%), and three extremities in 1 (2%) patient. Eleven (24%) patients did not need any fasciotomy at all. In the hemophan group, 11 fasciotomies were performed in 7 (88%) patients while one (12%) did not need fasciotomy. Twelve (67%) patients in the polysulfone group had 13 fasciotomies at different sites and 6 (33%) patients had none. Fasciotomies

Table 1
Demographical, biochemical, and hematological parameters of the groups

	All groups (n = 45)	Hemophan (n = 8)	Polysulfone (n = 18)	Combined (n = 19)	
Age (years)	33.9 ± 13.3	36.1 ± 13.4	37.2 ± 13.7	29.9 ± 12.4	NS
Sex (F/M)	24/21	5/3	10/8	9/10	NS
Time under rubble, hours	8.8 ± 3.8	10.3 ± 4.0	9.8 ± 4.4	7.5 ± 2.8	NS
BUN, mg/dL	81.0 ± 46.1	66.1 ± 24.1	89.1 ± 54.0	79.5 ± 45.3	NS
Creatinine, mg/dL	6.61 ± 3.54	3.81 ± 1.18	8.35 ± 4.05	6.13 ± 2.81	0.005
Potassium, meq/L	5.03 ± 1.28	5.09 ± 0.96	4.9 ± 1.55	5.07 ± 1.16	NS
Uric acid, mg/dL	7.1 ± 3.4	4.9 ± 1.1	8.0 ± 2.7	6.3 ± 4.5	NS
Calcium, mg/dL	7.1 ± 1.6	6.0 ± 1.7	7.7 ± 1.1	6.9 ± 1.9	NS
Phosphorus, mg/dL	5.7 ± 1.7	5.4 ± 1.0	6.3 ± 1.3	4.9 ± 2.1	NS
CK, U/L	21977 ± 28167	42462 ± 38807	11910 ± 27833	24077 ± 19214	0.036
LDH, U/L	1582 ± 1249	1714 ± 1499	1678 ± 1490	1435 ± 894	NS
AST, U/L	1055 ± 1586	876 ± 752	849 ± 1192	1331 ± 2111	NS
ALT, U/L	414 ± 642	338 ± 314	525 ± 873	333 ± 446	NS
Albumin, g/dL	2.6 ± 0.5	2.2 ± 0.7	2.6 ± 0.4	2.7 ± 0.4	NS
Leucocyte, /mm ³	12261 ± 4755	12760 ± 4891	12705 ± 4697	11710 ± 4976	NS
Hct, %	27.7 ± 6.9	29.8 ± 8.4	27.1 ± 5.2	27.4 ± 7.8	NS
Trombocyte, /mm ³	174761 ± 84455	153200 ± 48710	211666 ± 105876	145473 ± 52306	0.042
Fever, °C	37.9 ± 0.8	38.7 ± 1.1	37.6 ± 0.5	38.2 ± 0.7	NS
Systolic BP, mmHg	140.8 ± 30.6	126.8 ± 41.4	149.4 ± 30.1	138.6 ± 24.4	NS
Diastolic BP, mmHg	83.5 ± 17.4	76.2 ± 28.6	85.0 ± 14.6	85.2 ± 13.7	NS
Number of dialysis sessions	8.8 ± 6.1	3.7 ± 4.7	8.2 ± 5.7	11.4 ± 5.7	0.006
Number of HD days	10.7 ± 8.5	2.6 ± 1.2	10.3 ± 8.2	13.7 ± 8.6	0.014
Catheter number/ patient	1.28 ± 0.5	1 ± 0	1.27 ± 0.46	1.42 ± 0.6	NS
Urinary output, mL/day	664 ± 1711	1207 ± 1386	223 ± 368	869 ± 2428	NS
Hypotensive episode/session (%)	45.4 ± 6.5	67.5 ± 20	54.1 ± 5.4	36.9 ± 7.3	NS
Coagulation/session (%)	26.4 ± 18.3	33.7 ± 10.4	43.1 ± 5.4	23.0 ± 3.6	NS
Death	5 (11.1%)	2 (25.0%)	1 (5.5%)	2 (10.5%)	

Abbreviations: HD = hemodialysis, BP = blood pressure, Hct = hematocrit.

had to be performed in 20 different sites in 15 (79%) patients, while 4 (21%) patients did not need any in the combined group. There was no statistically significant difference between the groups with regard to fasciotomies performed ($p = 0.3$). Serum albumin levels were found to be lower and CPK levels higher in the patients who had fasciotomy.

Hemodialysis was indicated in 14 (31%) patients due to hypervolemia, azotemia, and hyperkalemia. Thirteen (29%) patients required hemodialysis therapy due to azotemia and hypervolemia and 7 (15%) patients due to azotemia and hyperkalemia. The indication for hemodialysis in 10 (23%) patients was only azotemia while one (2%) patient required hemodialysis due only to hypervolemia (see Table 2). There was no statistically significant difference between the indications of dialysis in all of the groups ($p > 0.05$).

Double lumen catheters were inserted by Seldinger technique to the subclavian vein in 33 (59%) patients, the jugular vein in 13 (23%) patients, and the femoral vein in 10 (18%) patients. The mean number of hemodialysis catheter used per patient was 1.28 ± 0.5 (1–3). Catheters were inserted eight times in the hemophan group, 23 times in the polysulfone group, and 27 times in the combined group. The number of catheters inserted was not significantly different between the groups.

Intermittent hemodialysis was performed with Baxter SPS550 machine in 34 (76%) patients, while Fresenius 4008/B machines were used in the remaining. The total number of IHD sessions was 396, and the mean number of sessions/patient was 8.8 ± 6.1 (1–22). Hemodialysis treatment continued for 10.7 ± 8.5 (1–36) days for each patient. In all, 408 dialyzers were used during IHD therapy (1.03/session); of which 86 (21%) was hemophan and the rest Fresenius 6 (F6).

A total of 30 IHD sessions (3.7 ± 4.7 session/patient) were performed for 2.6 ± 1.2 (1–4) days in the hemophan group. The total number of IHD sessions, the number of sessions/patient, and the mean duration of hemodialysis in the polysulfone and the combined groups were 149 vs. 218;

8.2 ± 5.7 (2–22) vs. 11.4 ± 5.7 (3–21); and 10.3 ± 8.2 (2–30) days vs. 13.7 ± 8.6 (4–36) days, respectively. There was no statistically significant difference between these two groups in regard to the number and duration of sessions.

All sessions were completed without any anticoagulation. Hypotension and coagulation of extracorporeal sets were the main intradialytic complications with rates of $45.4 \pm 6.5\%$ (13 patients) and 22% (10 patients), respectively. Both of these complications were present at the same time in 5 (11%) patients. During IHD, 51 units of pure red blood cells were infused to 25 (56%) patients, 16 units of fresh-frozen plasma were infused to 9 (20%) patients, and 24 units of 20% human albumin solutions were infused to a total of 7 (16%) patients.

In the hemophan group, only one patient (13%) received three units of pure red blood cells and one unit of fresh-frozen plasma. Thirty-two units of pure red blood cells were infused to 12 (67%) patients, 22 units of 20% human albumin solutions were infused to 6 (33%) patients, and 12 units of fresh-frozen plasma were infused to 6 (33%) patients in the polysulfone group. The number of transfusions in the combined groups was 16 units of pure red blood cells and three units of 20% human albumin solutions. The amount of blood transfused in the polysulfone group was significantly higher than the combined group ($p = 0.03$). There was no significant relation between coagulation of extracorporeal sets and the use of blood and its products, though intradialytic hypotension was found to be correlated with the transfusions ($r = 0.365$; $p = 0.014$). There was no correlation between hypotension and systolic and diastolic blood pressures at admission. The rates of hypotension and coagulation of extracorporeal sets was similar among all groups (see Table 1).

Five (11%) patients—2 (25%) in the hemophan group, 1 (5.5%) in the polysulfone group and 2 (10.5%) in the combined group—died, but there was no correlation between mortality rates and the type of the dialyzer used ($p = 0.344$). All patients without fasciotomy survived, while five (17%) of the patients with fasciotomy died.

Table 2
Hemodialysis indications of the groups

	All patients (n = 45)	Hemofan group (n = 8)	Polysulfone group (n = 18)	Combined group (n = 19)
Azotemia+hypervolemia+hyperkalemia	14	0	9	5
Azotemia+hypervolemia	13	3	5	5
Azotemia+hyperkalemia	7	1	3	3
Azotemia	10	4	1	5
Hypervolemia	1	0	0	1

Serum albumin ($p = 0.03$), systolic blood pressure ($p = 0.01$), diastolic blood pressure ($p = 0.018$), and thrombocyte count ($p = 0.003$) were found to be related to mortality. These values were lower in the deceased patients than those who survived. Age, sex, time under the rubble, BUN, serum creatinine, K, Ca, P, muscle enzymes, leukocyte and hematocrit levels, the type of the membrane used, temperature, presence of coagulation, and daily urine output were not correlated with mortality. The relationship between the mortality and hypotensive attacks was only mild ($p = 0.053$).

DISCUSSION

It is very difficult to perform a randomized study among crush syndrome patients, as all of them have to be evaluated in disastrous conditions. Therefore, our study was a retrospective analysis, and patients were not randomized to any membrane group. This is because during a disaster of this great magnitude, it is impossible to adjust the supplies. Also, you can only use the available material to the first presenters, and only then you can use the supplies provided to you by the local and international aids during the later days. It would be reasonable to expect some potentially important differences of basal characteristics among the study groups; there were significant differences in initial serum creatinine and CK levels.

In addition, trauma scales of patients are significantly different. Although no significant difference between the results of membrane groups has been reported, the APACHE II scoring system, which determines the severity of disease right before dialysis, would have provided more objective data.^[5,12]

No statistically significant difference was found between the demographic parameters of the patients when classified according to the type of dialyzer used. The time under the rubble was similar between the groups. The groups were not different from each other in terms of initial blood pressure, daily urine output, biochemical and hematological parameters, and fasciotomies.

There could be some technical problems while initiating renal replacement therapies in this group of patients, who are prone to develop coagulation problems.^[6,11,14] Conventional anticoagulation treatment during hemodialysis may cause bleeding, especially in traumatized patients who need surgical interventions.^[10] The use of tight or no heparin protocols during dialysis could decrease bleeding complications. Of course such an act could lead to some complications, such as coagulation of the extracorporeal sets, which was one of the main complications observed in our series. Another frequent complication was hypotension, which is known to occur in 15–40% of dialysis sessions.^[11]

The etiology of acute renal failure is a very important factor affecting the prognosis. Prognosis is worse if the patient has any other medical problems when compared with those who have no known disease at all.^[19,20] The mortality rate of acute renal failure due to rhabdomyolysis is high, ranging from 14 to 40%.^[21–25] The high mortality rate found in the hemophan group may be related to the low number of patients in that group. The relatively low overall mortality rate (11%) in our series led to the idea that the mortality of patients with acute renal failure due to crush syndrome can be low in case of early and vigorous follow-up.

In all, 70% of patients had oligo-anuria before onset of dialysis therapy. Oliguria is reported to have a negative effect on prognosis of acute renal failure, but our study did not confirm these reports.^[26,27] Lower serum creatinine levels at admission of patients in the hemophan group in our study may have a role on the shortness of the duration of hemodialysis therapy in that group.

Low serum albumin levels may be due to inflammation, capillary leakage, or hypervolemia. In the case of patients with crush syndrome, low serum albumin levels may cause larger amounts of myoglobin to be free and also more nephrotoxicity.^[21,28,29] There was a negative correlation between the number of traumatized extremities and serum albumin level.^[30] Mortality was higher among patients with low serum albumin levels. Hypoalbuminemia is known to increase mortality rates in acute renal failure caused by both crush syndrome and other reasons.^[20,31,32]

In this study, mortality was higher among patients with lower systolic and diastolic blood pressures at admission. Traumatization in a way that disturbs hemodynamic parameters may have increased the mortality in patients without co-morbid conditions. In addition, the relationship found between the mortality and the platelet count leads us to the idea that sepsis, multi-organ failure or disseminated intravascular coagulation may have developed in these patients. In addition to authors who prefer early fasciotomy, some think that this procedure increases morbidity and mortality by increased risk of infection.^[33] Higher fasciotomy rates of our patients may have increased indication for dialysis besides increasing the mortality, as all patients who died had this intervention.

In our series, the mean number of hemodialysis per patient was 8.9, while the mean duration during which hemodialysis support is necessary was 10.7 days. Our results are consistent with previously reported daily hemodialysis needs.^[34] The higher catabolic rate, serious hyperkalemia, and metabolic acidosis in patients with Crush syndrome necessitates more hemodialysis sessions.^[24,34]

The lower catheterization number in the hemophan group may be related to the shorter duration of hemodialysis in that group.

Enough evidence does not exist about which kind of membrane to be used in acute IHD of patients with acute renal failure secondary to crush syndrome. The complement-activating potential of biocompatible membranes is less, and this may decrease the number of dialysis sessions.^[4,5] However, conflicting results have been reported in studies involving acute renal failure patients.

In their prospective study, Gastaldello et al.^[13] found no difference between the duration of hemodialysis treatment in patients who were treated with IHD using semisynthetic membrane or the more biocompatible polysulfone membrane. Similarly, Kurtal et al.^[14] reported that biocompatible and bioincompatible membranes are not different in regard to duration of hemodialysis treatment and mortality. On the other hand, Schiffil et al.^[15] had reported in a retrospective study in which cuprophane and polysulfone membranes were compared, that results were better in polysulfone group. In meta-analysis and randomized studies, no significant difference was found between intradialytic complications and mortality of patient with chronic renal failure for whom either cellulose-based or synthetic membranes were used.^[16–18]

There are some limitations of our study, mainly small sample size. Patients' backgrounds were also different. These issues make the interpretation of the difference in mortality (five times higher in the hemophan group compared to the polysulfone group) impossible.

In this study, no effect of the type of dialysis membrane on outcome was detected in patients with crush syndrome who carry potential risks for intradialytic complications. Other potential factors, which may be responsible for the complications and mortality, should be investigated. Furthermore, this retrospective analysis might provide an insight to the preparedness for mass casualties in terms of the expected number of HD sessions and the preference of the dialyzers to be kept in stock.

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