Original Article

The 28-day survival rates of two cytokine-adsorbing hemofilters for continuous renal replacement therapy: a single-center retrospective comparative study

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Aim: Continuous renal replacement therapy (CRRT) with a cytokine-adsorbing hemofilter (CAH) is effective in the treatment of sepsis. Two filter types, namely polymethyl methacrylate (PMMA) and surface-treated AN69 (AN69ST) hemofilters, have been successfully used for CRRT, but no direct comparisons have been published to date. This study compared the efficacy, as measured by 28-day survival rates, of PMMA and AN69ST hemofilters in patients receiving CAH-CRRT.

Methods: This retrospective observational study reviewed the medical records of 142 patients who received CAH-CRRT between November 2013 and February 2015.

Results: The 28-day survival rates were higher in the AN69ST group than in the PMMA group for patients with or without sepsis (all patients, 79.4% versus 54.1%; patients with sepsis, 77.3% versus 50.0%; patients without sepsis, 83.3% versus 57.5%; $P < 0.05$). No significant differences were observed regarding 28-day survival rates of patients with or without sepsis (AN69ST, 77.3% versus 83.3%; $P = 0.51$; PMMA, 50.0% versus 57.5%; $P = 0.61$) using the same hemofilter.

Conclusion: The AN69ST hemofilter could be more effective than PMMA hemofilters for improving the survival outcomes of patients with or without sepsis.

Key words: Acute kidney injury, renal replacement therapy, retrospective study, sepsis

INTRODUCTION

SEPSIS IS A life-threatening condition characterized by organ dysfunction as a result of the dysregulated host response to infection.[1] Organ dysfunction occurs because of direct injury owing to bacterial infection as well as excessive inflammatory cytokine secretion triggered by the infection itself or by secondary cell damage due to the infection. This vicious positive feedback loop produces more inflammatory cytokines, leading to multiorgan dysfunction, consequently leading to death.[2,3]

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Blood purification therapies, such as high-volume hemofiltration[4] and endotoxin adsorption therapy using polymyxin-B-immobilized fiber column (PMX),[5] have been previously used to lower circulating inflammatory cytokines and prevent the continuous activation of the feedback loop. Nevertheless, no significant improvements in survival rates with high-volume hemofiltration therapy have been reported in several randomized control trials.[6–9] Large randomized control trials on PMX have also reported no improvements in prognosis,[10] casting doubt on the usefulness of PMX.

In Japan, continuous renal replacement therapy (CRRT) with a cytokine-adsorbing hemofilter (CAH) is a widely used blood purification method for the following reasons: (i) CAH can be used in any patients eligible for CRRT, (ii) there is no increase in replacement flow, and hence no increase in the treatment cost, (iii) blood coagulation is less likely to occur with CRRT compared with PMX therapy.

The polymethyl methacrylate (PMMA) hemofilter is a type of CAH with a larger pore size than commonly used

hemofilters. Nakada *et al.*[11] have analyzed 43 patients with septic shock who underwent PMMA-CRRT; the 28-day survival rate of these patients was 79.1%, and the ratio of overall and predicted survival (Os/Ps) was 2.41. Predicted survival was calculated using the Acute Physiology and Chronic Health Evaluation (APACHE) II score. These results suggest that the survival rates of patients with sepsis improved with PMMA-CRRT. Similar results have been documented in other previous reports.[12,13]

The surface-treated AN69 (AN69ST) hemofilter is another hemofilter that could be used for CAH-CRRT. Hirasawa *et al.*[14] have carried out CAH-CRRT using the AN69ST membrane in 34 patients with sepsis and have reported a high Os/Ps ratio of 3.24.

Although these previous reports have shown the efficacy of both types of hemofilter in improving the survival rates of patients with sepsis, no reports have directly compared these types. Thus, the aim of the study was to compare the 28-day survival rates of patients receiving CRRT with either an AN69ST or a PMMA membrane.

METHODS

Study design and patients

A RETROSPECTIVE OBSERVATIONAL study was carried out in which the medical records of patients who underwent CAH-CRRT at the Hachinohe City Hospital Emergency and Critical Care Center (Aomori) between November 2013 and February 2015 were reviewed. In our facility, CAHs are used for all patients requiring CRRT, unless contraindicated. Continuous renal replacement therapy was initiated according to the criteria described below, and the choice between the use of a PMMA membrane (HEMOFEEL CH-1.8W; Toray Medical Company, Tokyo, Japan) or AN69ST membrane (sepXiris 100; Baxter International, Chicago, IL, USA) was made by the treating physician.

Patients who presented with trauma (including extensive burns), drug poisoning, severe acute pancreatitis, or post-cardiopulmonary arrest, those in whom maintaining CAH-CRRT was difficult owing to circuit coagulation, or those who received therapy using a polymyxin B-immobilized fiber column were excluded. Patient data, including demographic, clinical, and laboratory data were acquired from the hospital database.

Study end-points

Patients were classified into two groups depending on the hemofilter used (AN69ST or PMMA) during treatment. The efficacy of CAH-CRRT in each group was evaluated by calculating Os (28-day survival rates) as well as Os/Ps ratio.

The primary end-point of the study was the difference in 28-day survival rate between the groups. The secondary end-point was the efficacy of the two hemofilter types in patients without sepsis. This efficacy was verified by comparing the 28-day survival rates between patients with and without sepsis.

Sepsis management

The diagnosis, initial treatment, and management of sepsis were undertaken according to the Surviving Sepsis Campaign Guidelines 2012.[15] The source of severe sepsis or septic shock was promptly removed, and adequate antibiotics were given. In case the shock state continued even after initial fluid resuscitation, norepinephrine was used as the first-choice vasopressor to maintain mean arterial pressure ≥65 mmHg. Intravenous hydrocortisone at a dose of 200 mg/day was used if adequate fluid resuscitation and vasopressor therapy were not able to restore hemodynamic stability. Patients did not receive any other anticoagulants, such as antithrombin for sepsis-associated disseminated intravascular coagulation or i.v. immunoglobulin for infection control.

Continuous renal replacement therapy setting

Continuous renal replacement therapy was initiated if the following conditions were observed in a patient: hyperkalemia, uremia, severe metabolic acidosis (pH < 7.2 in arterial blood gas analysis), congestive state, and a stage 3 or greater advanced acute kidney injury (AKI) according to the Kidney Disease: Improving Global Outcomes (KDIGO) Criteria. These criteria were used because serum creatinine levels were measured once daily; when urine output decreased, infused crystalloid volume increased to compensate for the intravascular volume deficiency in the first 24 h. Continuous renal replacement therapy was not initiated for non-renal indications, including the sole purpose of cytokine elimination. No strict criteria were established for CRRT discontinuation, and this decision was made by the treating physician on a case-by-case basis.

Continuous renal replacement therapy was carried out using continuous venovenous hemodiafiltration, with a 12-Fr vascular access catheter (Blood access UK-Catheter Kit; Nipro, Osaka, Japan) inserted through the right internal carotid vein. TR-525 and TR-55X (Toray Medical Company) blood purification systems were used. Continuous venovenous hemodiafiltration was initiated at a blood-side flow rate of 100–120 mL/min, filtration rate of 100 mL/h, and a

dialysis fluid-side flow rate of 500–1,500 mL/h (15 mL/kg/h). Sublood-BSG (Fuso Pharmaceutical Industries, Osaka, Japan) was used for both dialysate and substitution solutions. Nafamostat mesilate was used as an anticoagulant at a fixed infusion rate of 30 mg/h.

Statistical analysis

The χ^2-test and Fisher's exact test were used to compare qualitative variables. Student's *t*-test or the Mann–Whitney *U*-test was used to compare continuous variables. Kaplan–Meier survival curves were plotted for the AN69ST and PMMA groups, and the log–rank test was used to compare 28-day survival rates. Multivariate Cox regression analysis was also carried out with the 28-day survival rate as the dependent variable; $P < 0.05$ was considered statistically significant. All statistical analyses were undertaken using BellCurve 2 software (Social Survey Research Information, Tokyo, Japan).

RESULTS

FROM NOVEMBER 2013 to February 2015, 4,646 patients underwent treatment at our institution, of which 179 (3.9%) required CRRT, and 142 (3.1%) were finally included in our study (Fig. 1). Patients with sepsis accounted for 78 cases (54.9%) of the total cohort. These patients received CRRT when they met the KDIGO criteria of stage 3 or greater advanced AKI (68 cases; 87.2%). Another indication of CRRT included severe metabolic acidosis (five cases; 6.4%), postoperative control of chronic renal failure (five cases; 6.4%). The remaining 64 patients were without sepsis and received CRRT for severe metabolic acidosis (37 cases; 57.8%), hyperkalemia (21 cases; 32.8%), AKI (12 cases; 18.8%), uremia (three cases; 4.7%), postoperative control of chronic renal failure (two cases; 3.1%), and ischemia–reperfusion injury (two cases; 3.1%). Some patients presented with multiple indications for CRRT.

The 142 patients were classified into two groups according to the hemofilter used: AN69ST group ($n = 68$) and PMMA group ($n = 74$). Baseline patient characteristics are shown in Table 1. Significantly more cases of sepsis and serum lactic acid levels were observed in the AN69ST group than in the PMMA group.

The Os/Ps ratios in the AN69ST and PMMA groups were 2.61 and 1.61, respectively; the 28-day survival rate was higher in the AN69ST group than in the PMMA group (79.4% versus 54.1%; $P < 0.01$). Among patients with sepsis in both the AN69ST ($n = 44$) and PMMA ($n = 34$ cases) groups, Os/Ps ratios were 3.10 and 1.98 and the 28-day survival rate was significantly higher in the AN69ST group than in the PMMA group (77.3% versus 50.0%; $P < 0.05$). Among patients without sepsis in the AN69ST ($n = 24$) and PMMA ($n = 40$) groups, 28-day survival rates were 83.3% and 57.5% ($P < 0.05$) and Os/Ps ratios 2.12 and 1.42 ($P < 0.05$), respectively (Fig. 2).

A multivariate Cox regression analysis with the 28-day survival rate as the dependent variable produced a hazard ratio of 0.31 in favor of the AN69ST membrane compared with the PMMA membrane (95% confidence interval, 0.16–0.60; $P < 0.001$).

Figure 3 shows the 28-day survival rates of patients with and without sepsis using the same hemofilter. In the

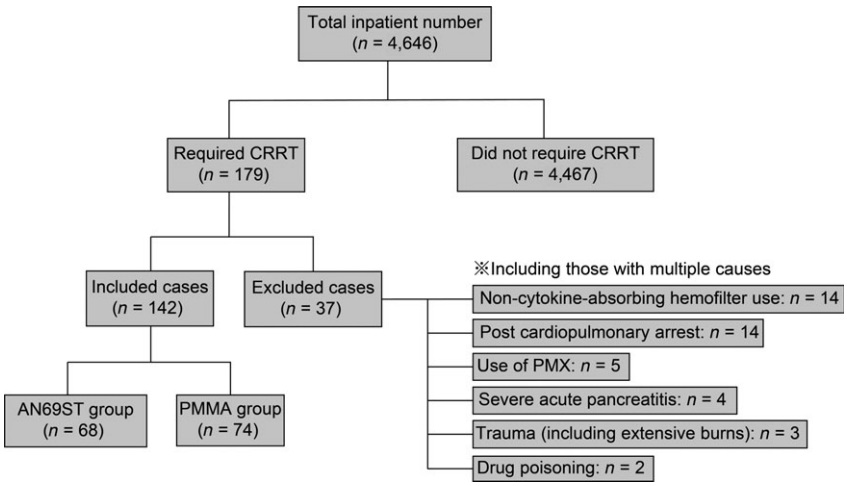

Fig. 1. Flowchart of patient recruitment to this study. AN69ST, surface-treated AN69; CRRT, continuous renal replacement therapy; PMMA, polymethyl methacrylate; PMX, polymyxin B-immobilized fiber column.

Table 1. Comparison of baseline characteristics among patients who underwent continuous renal replacement therapy (CRRT) with a polymethyl methacrylate (PMMA) or surface-treated AN69 (AN69ST) hemofilter

	Overall			Sepsis patients			Non-sepsis patients		
	AN69ST group (n = 68)	PMMA group (n = 74)	P-value	AN69ST group (n = 44)	PMMA group (n = 34)	P-value	AN69ST group (n = 24)	PMMA group (n = 40)	P-value
Age (years)	80 (67–85)	76 (67–81)	0.24	82 (68.5–86)	76 (72–80.8)	0.13	72.5 (66–81.3)	76 (66.5–82.3)	0.21
Male : female	41:27	46:28	0.48	22:22	22:12	0.29	19:5	24:16	<0.05
APACHE II score	30 (24–34)	29 (25–35)	0.98	31 (25–34)	32 (28–36)	0.88	29 (23–36)	29 (24–35)	0.87
SOFA score	15 (12–15)	14 (11–15)	0.12	15 (14–16)	15 (13–17)	0.32	13 (10–15)	13 (8–14)	0.13
Catecholamine index[†]	15.0 (0.0–39.9)	17.5 (0.0–48.0)	0.60	25 (10.5–50.3)	17.5 (0.0–35)	0.53	2.3 (1.5–5.4)	7.5 (0.0–24.3)	0.09
Leukocyte count (/μL)	12,600 (6,250–18,850)	12,900 (8,900–17,300)	0.61	9,750 (5,375–18,125)	12,650 (8,075–19,625)	0.43	14,700 (10,275–19,550)	13,300 (9,600–16,150)	0.29
Serum creatinine (mg/dL)	2.18 (1.33–3.77)	2.74 (1.75–3.78)	0.07	1.81 (1.15–3.7)	2.18 (1.49–3.47)	0.66	2.42 (1.94–4.07)	3.05 (2.24–4.54)	0.43
Serum lactate (mmol/L)	3.3 (1.6–5.2)	1.9 (1.3–6.8)	<0.05	3.3 (2–5.2)	1.8 (1.2–4.4)	0.87	2.5 (1.5–5.35)	1.9 (1.38–7.3)	0.23
BNP (pg/mL)	290.8 (160.4–504.6)	351.4 (130.2–756.2)	0.22	315.3 (170.9–500.9)	206.1 (82.9–445.3)	0.76	256.2 (61.3–496.4)	616.2 (189.7–1159.9)	<0.05
Ejection fraction (%)	53 (43–62)	57.5 (45–65)	0.59	53 (41–63)	59 (46–64)	0.50	53 (46–59)	56 (40–67)	0.88
Sepsis	44 (64.7%)	34 (45.9%)	<0.05	44 (100.0%)	34 (100.0%)	NA	0 (0.0%)	0 (0.0%)	NA
Abdominal	21 (47.7%)	17 (50.0%)	0.62	21 (47.7%)	17 (50.0%)	0.51	NA	NA	NA
Respiratory	9 (20.5%)	6 (17.6%)	0.51	9 (20.5%)	6 (17.6%)	0.18	NA	NA	NA
Urinary tract	9 (20.5%)	3 (8.8%)	0.18	9 (20.5%)	3 (8.8%)	0.54	NA	NA	NA
Bone and soft tissue	3 (6.8%)	3 (8.8%)	0.76	3 (6.8%)	3 (8.8%)	0.54	NA	NA	NA
Vascular catheter infection	0 (0.0%)	1 (2.9%)	0.44	0 (0.0%)	1 (2.9%)	0.44	NA	NA	NA
Bacteremia (unknown source)	1 (2.3%)	3 (8.8%)	0.24	1 (2.3%)	3 (8.8%)	0.24	NA	NA	NA
Unknown	1 (2.3%)	1 (2.9%)	0.68	1 (2.3%)	1 (2.9%)	0.69	NA	NA	NA
Kidney									
Acute kidney injury	55 (80.9%)	62 (83.8%)	0.65	36 (81.8%)	32 (94.1%)	0.80	19 (79.2%)	30 (75.0%)	0.95
CKD	6 (8.8%)	7 (9.5%)	0.57	3 (6.8%)	2 (5.9%)	0.19	3 (12.5%)	7 (17.5%)	0.47
CKD on hemodialysis	7 (10.3%)	5 (6.8%)	0.35	5 (11.4%)	0 (0.0%)	0.36	2 (8.3%)	3 (7.5%)	0.63
CRRT duration (h)	36.5 (26.3–43.3)	29.5 (19.6–43.7)	0.11	31.3 (19.3–44.6)	31.3 (19.3–44.6)	0.21	36.8 (30.9–45.1)	28.7 (21.3–40.1)	0.17
CRRT discontinuation	47 (77.0%)	36 (52.2%)	0.13	30 (76.9%)	17 (53.1%)	<0.05	17 (77.3%)	19 (51.4%)	<0.05

[†]Catecholamine index (μg/kg/min) = infusion rates of (dopamine + dobutamine + [noradrenaline + adrenaline]) × 100.
APACHE, Acute Physiology and Chronic Health Evaluation; BNP, brain natriuretic peptide; CKD, chronic kidney disease; NA, not applicable; SOFA, Sequential Organ Failure Assessment.

AN69ST group, the patient variables of age, sex ratio, Sequential Organ Failure Assessment (SOFA) score, and catecholamine index were significantly different ($P < 0.05$) between patients with sepsis compared with those without sepsis. There were no statistically significant differences in other characteristics. Similarly, in the PMMA group, only the SOFA score, serum creatinine levels, and the proportion of patients with chronic kidney disease were significantly different ($P < 0.05$). Within the same hemofilter group, the 28-day survival rates did not differ between patients with and without sepsis.

DISCUSSION

IN THIS STUDY, the 28-day survival rate significantly improved with the use of AN69ST membrane compared with the PMMA membrane. This result might not be possible to compare simply with previous trials because the CRRT setting, such as initiation and withdrawal criteria, hemofilter, and purification dose are different from each trial. In our facility, CRRT was initiated for the patients with hyperkalemia, uremia, severe metabolic acidosis, congestive state, and AKI stage 3 of the KDIGO criteria; these criteria were similar to those used in many previous reports. The decision to discontinue CRRT was made by the treating physician on a case-by-case basis. We have emphasized the serum lactic acid value, which can be easily measured, to decide CRRT discontinuation. Even if oliguria continues, CRRT is withdrawn using the serum lactic acid value ≤4 mmol/L as the index if other reasons for the introduction of CRRT, such as metabolic acidosis and hyperkalemia, are improved. In previous studies verifying the efficacy of CRRT, the duration was from 4 to 6 days.[7,9,16] Even in a study restricting the patient's background to sepsis, the CRRT duration was 99 ± 57.8 h,[17] which is long compared to this study. However, many of these studies adopted an

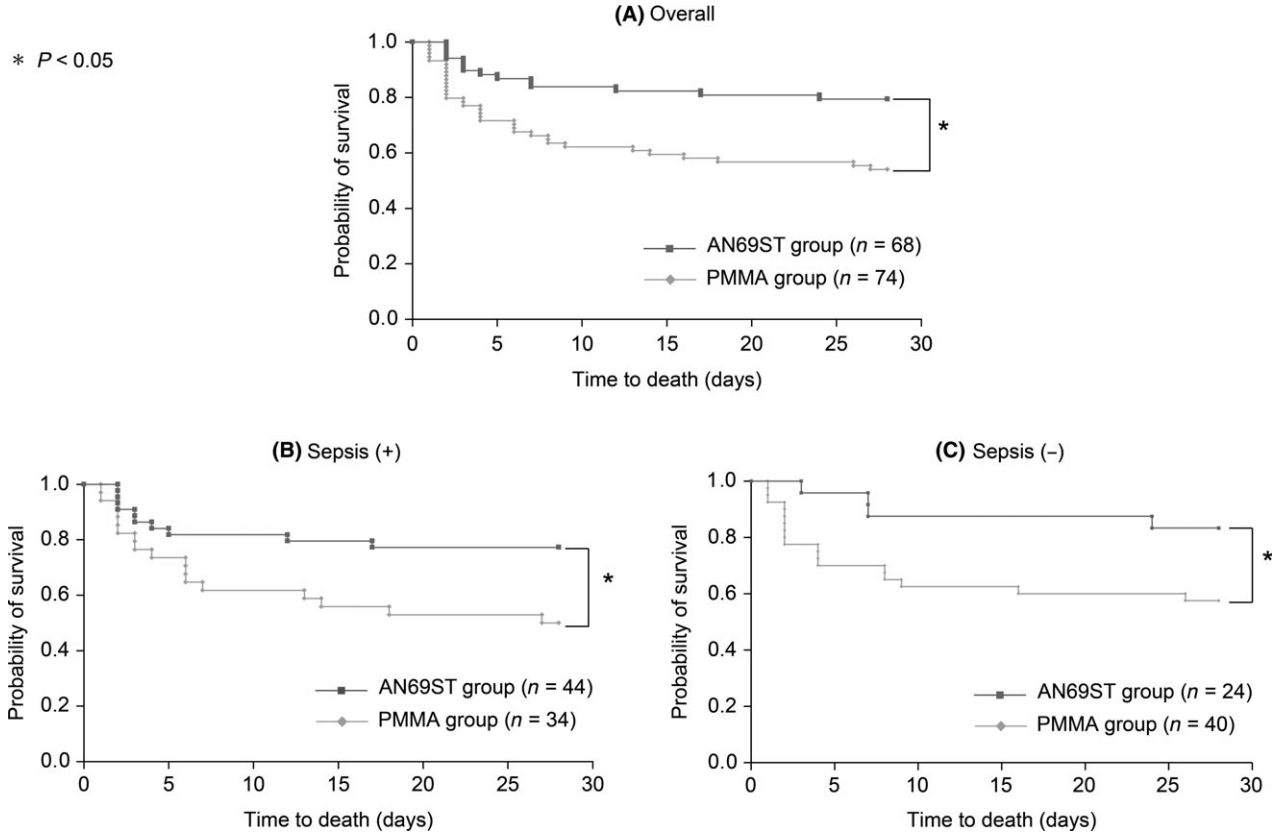

Fig. 2. Kaplan–Meier curves comparing 28-day survival rates among patients who underwent continuous renal replacement therapy (CRRT) with a surface-treated AN69 (AN69ST) or polymethyl methacrylate (PMMA) filter. The AN69ST group showed higher 28-day survival rates than the PMMA group for patients with and without sepsis. A, All patients, 79.4% versus 54.1%, respectively. B, Septic, 77.3% versus 50.0%, respectively. C, Non-septic, 83.3% versus 57.5%, respectively. $P < 0.05$.

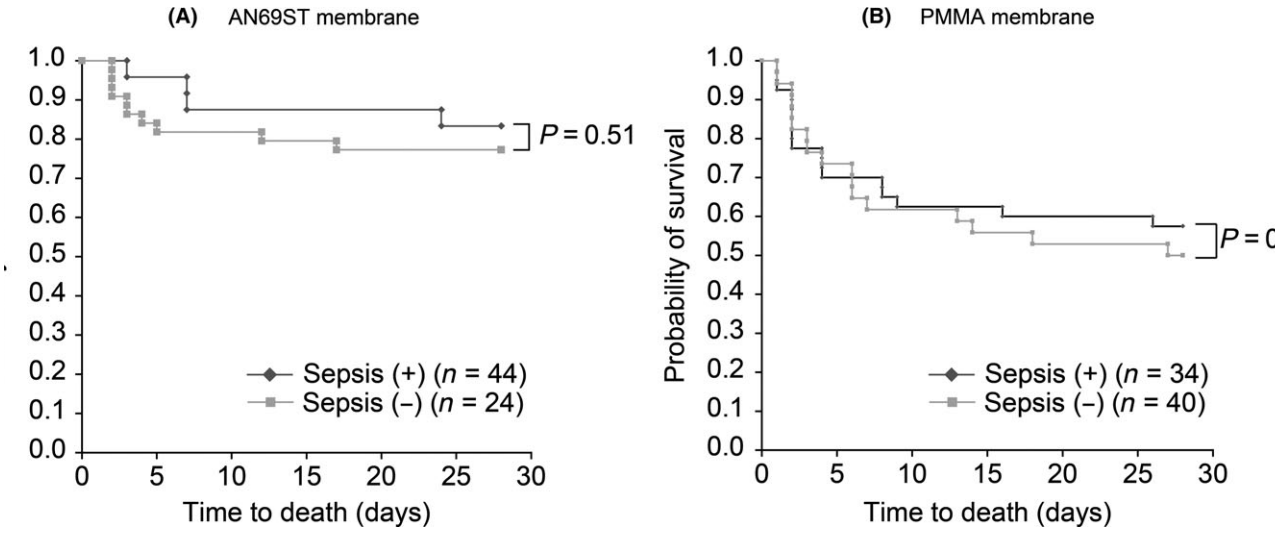

Fig. 3. Kaplan–Meier curves comparing 28-day survival rates of patients who underwent continuous renal replacement therapy, with or without sepsis, using a surface-treated AN69 (AN69ST) or polymethyl methacrylate (PMMA) hemofilter. For patients using AN69ST, the 28-day survival rate was 77.3% in patients with sepsis versus 83.3% in those without sepsis ($P = 0.51$). For patients using PMMA, the 28-day survival rate was 50.0% in patients with sepsis versus 57.5% in patients without sepsis ($P = 0.61$).

increase in urine volume as a criterion for CRRT discontinuation. Thus, CRRT discontinuation criteria vary between each facility and remain vague.

Although patients were in a critical condition, with APACHE II scores of approximately 30, the 28-day survival rate of the whole cohort was comparable with that previously reported.[11,14]

This study suggests the efficacy of CAH-CRRT regardless of the presence or absence of sepsis. There are several reasons contributing to this result. As previously mentioned, although both AN69ST and PMMA membranes make use of the adsorption principle, the adsorption methods used are different. The PMMA membrane primarily removes cytokines by adsorption to the hemofilter membrane matrix and has the disadvantage of proportionality between the degree of adsorption and membrane size, and its efficacy decreases with time.[18] Conversely, th AN69ST membrane has a bulky layer and uses ionic bonding by means of strong negative electric charges as the adsorption method. Moreover, adsorption occurs throughout the membrane matrix rather than at the contact surface alone owing to its hydrogel structure with 70% moisture, making its adsorption volume extremely large.[19] Reportedly, the AN69ST membrane shows two-fold greater absorption for high-mobility group box 1 protein than the PMMA membrane.[20] Another study has documented that the AN69ST membrane has the potential to eliminate cytokines in pigs with sepsis.[21] Thus, this difference in adsorption capability might have produced higher survival rates observed in the AN69ST group. Furthermore, the AN69ST membrane has been shown to significantly adsorb fibroblast growth factor 23, which has been recently shown to be associated with heart failure.[22] Therefore, the observed improvement in survival during morbid states could be due protection against heart failure secondary to fibroblast growth factor 23 adsorption.

The observation that equivalent results were obtained for patients with and without sepsis was remarkable. A previous study has reported that CAH-CRRT is effective for treating non-septic acute pancreatitis.[23] These data could indicate that CAH-CRRT is an effective treatment for patients without sepsis requiring treatment due to conditions arising from excessive inflammatory reactions.

LIMITATIONS

OUR STUDY HAS some limitations. First, the main limitation is the single-center retrospective observational design of the study. Thus, there might be many confounding factors other than the CRRT membrane affecting survival rates, such as selection bias of cases, CRRT setting, and the timing of the start or discontinuation of CRRT. The sample size was small as the study was undertaken in a single center. Second, CAH was used for all patients with the introduction of CRRT at our facility; therefore, comparing them with patients undergoing non-CAH-CRRT approaches as a control group was not impossible. Finally, biomarkers, such as interleukin levels, could not be routinely evaluated owing to their high cost at our facility. Future prospective

multicenter randomized controlled trials are warranted to verify our results. In doing those trials, patients' background and the criteria for CRRT initiation or discontinuation should be aligned with previous trials so that they can be compared.

CONCLUSION

OUR RETROSPECTIVE EVALUATION of the efficacy of AN69ST and PMMA membranes during routine CRRT showed a significant difference in 28-day survival in favor of the cohort that received CRRT with AN69ST. No significant differences were observed in 28-day survival rates of patients with and without sepsis using the same hemofilter. These results suggest the efficacy of CAH-CRRT for all conditions other than sepsis that cause an inflammatory reaction.

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DISCLOSURE

Approval of the research protocol: This study protocol was approved by the Hachinohe City Hospital Ethics Committee (approval no. 1516).
Informed consent: The need for informed consent was waived by the Hachinohe City Hospital Ethics Committee owing to the retrospective observational design of the study.
Registry and the registration no. of the study/trial: N/A.
Animal Studies: N/A.
Conflict of interest: The authors declare that they have no conflicts of interest.

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