

THE EFFECT OF CONTINUOUS RENAL REPLACEMENT THERAPY WITH THE AN69ST MEMBRANE ON INFLAMMATORY MARKERS AND THE LEVEL OF CONSCIOUSNESS OF HEMODIALYSIS PATIENTS WITH STROKE: COMPARISON WITH HEMODIALYSIS WITH LOW BLOOD FLOW RATE

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ABSTRACT

Introduction: Hemodialysis (HD) with low blood flow rate, continuous renal replacement therapy (CRRT), and peritoneal dialysis are recommended for patients with stroke complications to prevent intracranial hypertension because of the low diffusion capacity of the brain barrier. However, detailed guidelines are not currently available; thus, there is an urgent need to establish such guidelines.

Material and Methods: We developed a novel protocol for performing CRRT with the AN69ST membrane, which has excellent adsorption capacity for various cytokines. The objective of this study was to compare the effect of the novel protocol with that of the current standard protocol, i.e. hemodialysis with low blood flow rate. To compare the effect of hemodialysis with low blood flow (HD group, n=27) and CRRT with AN69ST membrane (CRRT group, n=8), we measured the following consciousness and blood inflammatory parameters in patients with stroke complications at baseline and after 1 week of treatment: Glasgow Coma Scale (GCS) score, C-reactive protein (CRP) levels, and white blood cell (WBC) and platelet count.

Results: After 1 week, the total GCS score did not improve in the HD group, but improved significantly in the CRRT group (HD group: 13.1±3.0 to 13.3±3.1, p=0.5508, CRRT group: 8.9±3.9 to 11.5±3.9, p=0.0313). Improvement in the CRRT group was significantly higher than in the HD group (p=0.0039). CRP levels did not change significantly in either the HD (3.8±5.5 to 5.3±4.3 n.s.) or CRRT groups (7.7±10.0 to 3.7±3.2 n.s.); however, they tended to increase in the HD group and decrease in the CRRT group. No significant changes were observed in WBC and platelet counts after 1 week of treatment in either group.

Conclusion: CRRT with the AN69ST membrane might have a beneficial effect on the consciousness level and inflammation of patients with stroke.

Keywords: Hemodialysis, Stroke, CRRT, AN69ST

INTRODUCTION

Patients undergoing chronic maintenance dialysis generally have a higher incidence of cerebrovascular events than healthy people do, and the prognosis for these patients is often unfavorable when such events occur as a complication during dialysis. [1] The Dialysis Outcomes and Practice Pattern Study (DOPPS), which analyzed data from patients undergoing dialysis in Japan, Europe, and the United States, revealed that the prevalence of cerebrovascular disorders in these patients was between 12.5% and 18.4%. [2] In Japan, the incidence of cerebral hemorrhage among patients undergoing chronic maintenance dialysis is reported to be 3.0–10.3 cases per 1,000 patients per year, a rate that is extremely high compared with the general Japanese population, 1.2–3.2 cases per 1,000 people per year. [3–7] Moreover, the mortality rate among dialysis patients who have developed cerebral hemorrhage as a complication is 27–83% (average: 53%), which is higher than the 19% mortality rate in the general population. [7] Thus, there is an urgent need to reduce the incidence of cerebrovascular events in these patients in order to improve outcomes.

The selection of a blood purification therapy is a critical factor in improving the poor prognoses in patients undergoing dialysis. As the risk of hematoma increases within the first 24 hours after the onset of cerebral hemorrhage, avoiding dialysis is desirable during this period. [8] In addition, when hemodialysis is unavoidable, the attending physician should select a method that has a minimal effect on intracranial pressure. Krane investigated the intracranial pressure fluctuations in patients with cerebral hemorrhage by comparing patients undergoing hemodialysis (HD) and those undergoing peritoneal dialysis, and found that intracranial pressure rose sharply in patients undergoing HD, but remained stable in patients undergoing peritoneal dialysis. [9] In addition, Davenport compared intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT), and reported that intracranial pressure increased in patients undergoing IHD but not in patients undergoing CRRT. [10] Peritoneal dialysis, reduced blood flow dialysis, and CRRT are recommended in the Japanese treatment guidelines for stroke as well as the treatment guidelines published by The Japanese Society for

Dialysis Therapy. [1, 11] However, the precise indications for each of these therapies have not been established. There are also numerous institutions that are unable to adequately provide peritoneal dialysis and CRRT because of staffing and resource limitations. Until 2016, only dialysis with a low blood flow rate could be employed at our institution because of staffing limitations; however, CRRT became feasible as a result of the increase in our staff in 2017. Furthermore, because many patients with stroke also develop infection, we must manage infection and intracranial pressure hypertension simultaneously. The AN69ST membrane was first approved by the Japanese Health Insurance System (JHIS) in 2014 for use in patients with severe sepsis and septic shock.

Therefore, we developed a new dialysis protocol, CRRT with AN69ST membrane, and compared it with hemodialysis with low blood flow, with respect to the levels of consciousness and inflammation markers.

MATERIAL AND METHODS

The purpose of this study was to investigate the change in symptoms of cerebrovascular disease between the HD group, in which dialysis with low blood flow rate, and the CRRT group, which followed the new protocol.

This study was approved by the Institutional Review Board of the Hanwa Memorial Hospital.

Details regarding the previous standard and new study protocols are provided below. Both protocols were performed in patients undergoing chronic maintenance dialysis who were admitted to our hospital because of cerebrovascular diseases (e.g., stroke, but excluding lacunar infarction), and who were subsequently admitted to the intensive care unit (ICU) or high care unit (HCU).

Previous protocol (HD group)

The patients, dialysis with low blood flow rate was employed.

New protocol (CRRT group)

Patients received CRRT with the AN69ST membrane 3–4 times a week as follows:

- Patients under mechanical ventilation support: CRRT for 24 hours/day

• Patients without mechanical ventilation: CRRT for up to 8 hours/day

The HD group comprised 27 patients who were admitted in 2015 and 2016. The CRRT included 8 patients who were admitted from November 2017 to April 2018.

The patients' level of consciousness was evaluated using the Glasgow Coma Scale (GCS), which assesses the consciousness of patients by evaluating their visual, verbal, and motor functions. The following parameters were compared between the HD and CRRT groups: GCS score, CRP level, and WBC and platelet counts at baseline and after 1 week of treatment.

Statistical analysis was conducted using the JMP® 12 software suite (SAS Institute Inc., Cary, NC, USA). The Wilcoxon rank-sum test was used for unpaired data, Wilcoxon signed-rank test was used for paired data, and Fisher's exact test was used to evaluate category variables. The level of statistical significance was set at a hazard ratio of 5%. Results were expressed as mean $\pm$ standard deviation or median (25, 75%).

RESULTS

No significant differences were observed between the CRRT and HD groups with respect to patient demographic and clinical data (Table 1). The dialysis conditions in the HD and CRRT groups are described in Table 2. No improvement in the total GCS score was observed in the HD group, but in the CRRT group, level of consciousness improved after 1 week of treatment [Fig.1a]. A significant difference was

also observed in comparisons between the HD and CRRT groups with regard to the extent of change in GCS score from baseline through the end of 1 week of treatment [Fig. 1b]. With regard to changes individual elements of the GCS score over baseline values, the level of improvement in "eye opening" was significant in the HD group, with no significant changes observed in the CRRT group [Fig. 2a]. Comparison between the two groups revealed that the extent of improvement in "eye opening" and "best verbal response" in the CRRT group was significantly greater than that in the HD group [Fig. 2b]. No significant difference in CRP level was observed between at baseline and after treatment in neither groups; however, a worsening trend was observed in the HD group, while an improving trend was observed in the CRRT group (HD group: 3.8 ± 5.5 mg/dl before dialysis, 5.3 ± 4.3 mg/dl after 1 week of treatment; CRRT group: 7.7 ± 10.0 mg/dl before dialysis, 3.7 ± 3.2 mg/dl after 1 week of treatment) [Fig. 3a]. In addition, the degree of reduction in CRP values in the CRRT group was significantly greater than that in the HD group ($p=0.0477$) [Fig. 3b].

No significant improvement was observed between baseline and post-treatment values in each group and in the extent of change after treatment between the two groups with respect to WBC (HD group: $8,657 \pm 3,274/\mu\text{L}$ before dialysis, $7,807 \pm 1,970/\mu\text{L}$ after 1 week of treatment; CRRT group: $11,886 \pm 3,046/\mu\text{L}$ before dialysis, $8,971 \pm 3,657/\mu\text{L}$ after 1 week of treatment) or platelet count (HD group: $187,857 \pm 84,169/\mu\text{L}$ before dialysis, $206,288 \pm 83,259/\mu\text{L}$ after 1 week of treatment; CRRT group: $170,857 \pm 33,672/\mu\text{L}$ before dialysis, $194,429 \pm 48,686/\mu\text{L}$ after 1 week of treatment).

Table 1. Patient characteristics and clinical conditions

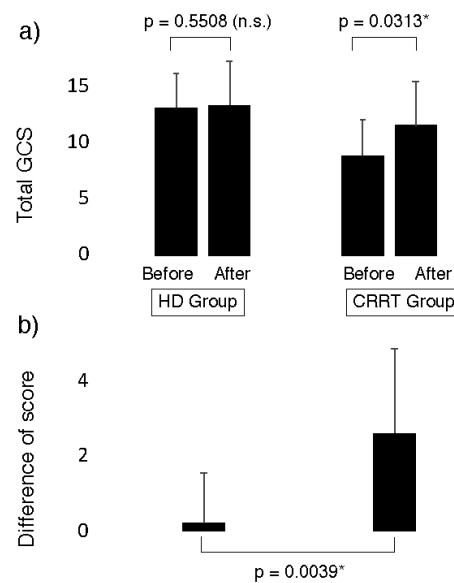
Characteristics and clinical conditions	HD (n=27)	CRRT (n=8)	P value
Age, mean (SD) (years)	64.9 (12.2)	68.4 (8.7)	0.4913
Male : Female, n	17 : 10	6 : 2	0.6855
Weight, mean (SD) (kg)	53.1 (13.2)	58.0 (23.0)	0.4475
Diabetes mellitus, n	19	7	0.6478
Surgery, n	3	3	0.117
Brain hemorrhage, n	13	6	0.2438
Subarachnoid hemorrhage, n	1	1	0.4101
Brain infarction, n	13	1	0.1078
Mechanical ventilation, n	3	2	0.5675
BUN, mean (SD) (mg/dl)	49.9 (19.3)	59.8 (15.8)	0.095

CRRT, continuous renal replacement therapy; HD, hemodialysis; BUN, blood urea nitrogen; SD, standard deviation.

Table 2. *Dialysis conditions*

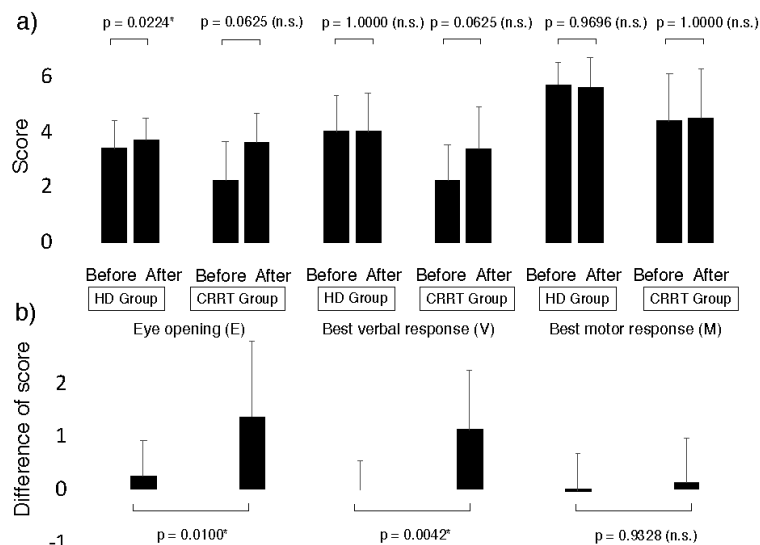
Dialysis conditions	HD (n=27)	CRRT (n=8)
Blood pump flow rate, median (25, 75%) (ml/min)	200 (150, 250)	100 (100, 108)
Dialysate flow rate, median (25, 75%) (ml/min)	500 (500, 500)	49 (13, 300)
Dialysis time, mean (SD) (time)	3.9 (0.4)	8.8 (6.2)
AN69ST: other membranes, n	0 : 27	8 : 0
CRRT, n	0	8
Conventional hemodialysis, n	26	0
Hemodiafiltration, n	1	0
Effective membrane area, median (25, 75%) (m ²)	1.5 (1.5, 1.8)	1 (1, 1.375)

CRRT, continuous renal replacement therapy; HD, hemodialysis

**Figure 1.** *a) Comparison of total Glasgow Coma Scale (GCS) scores between the hemodialysis (HD) and continuous renal replacement therapy (CRRT) groups before and after 1 week of treatment.*

b) Comparison of the extent of change in GCS score between the two groups.

Asterisk indicates $p < 0.05$ on the Wilcoxon rank-sum test and the Wilcoxon signed-rank test. n.s. indicates a non-significant difference.

**Figure 2.** *a) Comparison of scores on individual components of the Glasgow Coma Scale (GCS) between the hemodialysis (HD) and continuous renal replacement therapy (CRRT) groups before and after 1 week of treatment.*

b) Comparison of the extent of change in individual component GCS scores between the two groups.

Asterisk indicates $p < 0.05$ on the Wilcoxon rank-sum test and the Wilcoxon signed-rank test.

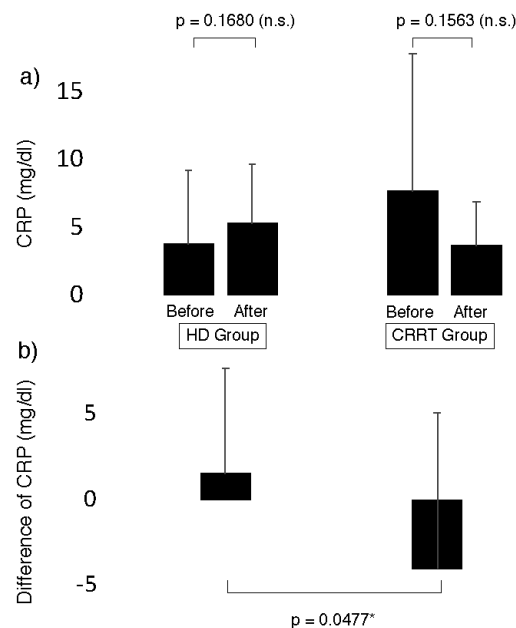


Figure 3. a) Comparison of C-reactive protein (CRP) levels between the hemodialysis (HD) and continuous renal replacement therapy (CRRT) groups before and after 1 week of treatment. b) Comparison of the extent of change in CRP levels between the two groups. Asterisk indicates $p < 0.05$ on the Wilcoxon rank-sum test and the Wilcoxon signed-rank test.

DISCUSSION AND CONCLUSION

A small number of reports have indicated that dialysis with low blood flow rate does not result in increased intracranial pressure; however, in the present study, patients' levels of consciousness and CRP levels improved more in the CRRT group than in the HD with reduced low blood flow group. [12]

Although membranes permitted for hemofiltration during CRRT in Japan include polysulfone, cellulose triacetate, polyethersulfone, and polymethylmethacrylate (PMMA), CRRT using the AN69ST membrane was approved for coverage by the JHIS in 2014. Among these filtration membranes, only PMMA and AN69ST are capable of cytokine adsorption. PMMA excels at adsorbing cytokines of approximately 20 kDa via monomolecular layer fitting. [13] In contrast, as the AN69ST membrane achieves adsorption via electric potentials, it is thought to be capable of strongly adsorbing positively-charged cytokine molecules. The theoretical capacity of membranes to remove cytokines according to their electrical potentials and molecular weights are shown in [Fig. 4], which shows that the AN69ST membrane has a broader adsorption capacity. [14] A study in which the efficacy of the AN69ST membrane was compared with that of PMMA

in sepsis patients, CRRT using the AN69ST membrane was significantly more effective in the early stabilization of vital signs. [15] In addition, previous studies have shown that CRRT with AN69ST in sepsis patients achieved superior improvement in mortality rate according to predictions based on their Acute Physiology and Chronic Health Evaluation (APACHE) score. [16, 17] Furthermore, according to "the peak concentration hypothesis" proposed by Ronco et al., the capacity for adsorption of a wide range of cytokines is advantageous during sepsis treatment. [18] In our clinical practice, we observed numerous cases in which patients on chronic maintenance dialysis developed high CRP levels. Therefore, we assumed that the use of the AN69ST membrane would have a positive effect on chronic hemodialysis patients with stroke. In addition, even though three subjects in the CRRT group underwent dialysis with procedures close to those of conventional hemodialysis (dialysis fluid flow rate of 300 ml/min, blood flow rate of 100 ml/min, and dialysis period of 6 hours), the improvement observed in the CRRT group is nevertheless believed to be the result of the cytokine adsorption capability of the AN69ST membrane.

CRRT with the AN69ST membrane might have a beneficial effect on the consciousness level and inflammation of patients with stroke.

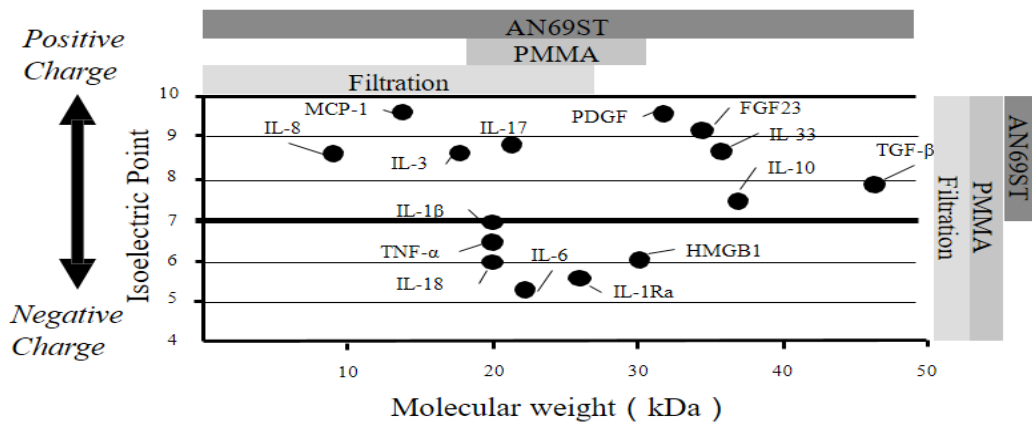


Figure 4. Cytokine removal characteristics of different membrane materials

The respective cytokine removal characteristics of filtration, polymethylmethacrylate (PMMA), and the AN69ST are shown. The Y-axis indicates the electrical potential and the X-axis indicates the molecular weight.

Author contributions

Conceptualization, Methodology & Curation: Matsui, Nakagawa. Analysis: Matsui, Kikuchi. Writing – review & editing: Matsui, Horio. Supervision & Validation: Horio, Hashimura.

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Резиме

ЕФЕКТОТ НА КОНТИНУИРАНА БУБРЕЖНА ЗАМЕСТИТЕЛНА ТЕРАПИЈА СО МЕМБРАНАТА AN69ST ВРЗ ВОСПАЛИТЕЛНИТЕ МАРКЕРИ И НИВОТО НА СВЕСНОСТ КАЈ ПАЦИЕНТИТЕ НА ХЕМОДИЈАЛИЗА СО МОЗОЧЕН УДАР: СПОРЕДБА СО ХЕМОДИЈАЛИЗА СО НИЗОК ПРОТОК НА КРВ

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Вовед: Хемодијализата (HD) со низок проток на крв, континуираната бубрежна заместителна терапија (CRRT) и перитонеалната дијализа се препорачуваат кај пациенти со компликации од мозочен удар за да се спречи интракранијална хипертензија поради нискиот дифузен капацитет на мозочната бариера. Сепак, во моментов не се достапни детални упатства; оттука, постои итна потреба да се утврдат вакви упатства.

Материјали и методи: Развивме нов протокол за изведување на CRRT со мембраната AN69ST, која има одличен апсорпциски капацитет за различни цитокини. Целта на оваа студија беше да се спореди ефектот на новиот протокол со оној на постојниот стандарден протокол, односно хемодијализа со низок проток на крв. За да се спореди ефектот на хемодијализа со низок проток на крв (HD група, $n = 27$) и CRRT со мембрана AN69ST (CRRT група, $n = 8$), ги меревме следниве параметри за свесност и крвни инфламатори кај пациенти со компликации од мозочен удар на почетокот и по една недела од третманот: вредност од Glasgow Coma Scale (GCS), нивоа на С-реактивен протеин (CRP), број на бели крвни клетки (WBC) и на тромбоцити.

Резултати: По една недела вкупната вредност на GCS не се подобри во групата HD, но значително се подобри во групата CRRT (HD група: $13,1 \pm 3,0$ до $13,3 \pm 3,1$, $p = 0,5508$, група CRRT: $8,9 \pm 3,9$ до $11,5 \pm 3,9$, $p = 0,0313$). Подобрувањето во групата CRRT беше значително повисоко отколку кај групата HD ($p = 0,0039$). Нивоата на CRP не се промениле значајно ниту кај HD ($3,8 \pm 5,5$ до $5,3 \pm 4,3$ n.s.) или групите CRRT ($7,7 \pm 10,0$ до $3,7 \pm 3,2$ n.s.); сепак, тие имаат тенденција да се зголемат во групата HD и да се намалат во групата CRRT. Не се забележани значајни промени во бројот на белите крвни зрна и тромбоцитите по една недела од третманот во која било група.

Заклучок: CRRT со мембраната AN69ST може да има корисен ефект на нивото на свесноста и воспалението кај пациентите со мозочен удар.

Клучни зборови: хемодијализа, мозочен удар, CRRT, AN69ST