

Effect of Sodium Balance and the Combination of Ultrafiltration Profile during Sodium Profiling Hemodialysis on the Maintenance of the Quality of Dialysis and Sodium and Fluid Balances

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Excessive sodium gain is a major hindrance of sodium profiling hemodialysis (HD) that offsets the benefit in reducing intradialytic hypotension-related discomforts (IHD). Patients who showed frequent IHD (>30% of the sessions; $n = 11$) were enrolled in a prospective study that consisted of two phases. In the phase 1 study, eight treatment modalities were evaluated: Conventional HD (control), sodium balance–positive step-down sodium profiling HD (PS), sodium balance–neutral step-down sodium profiling HD (NS), sodium balance–neutral alternating sodium profiling HD (NA) without ultrafiltration (UF) profile, and all those with UF profile (UF only, PS+U, NS+U, and NA+U). The incidences of “dialysis failure,” defined as the occurrence of one or more of (1) session failure (discontinuation of session <75% of planned time), (2) UF failure (%UF achieved <70%), and (3) delivery failure ($Kt/V < 1.1$), were 48.5, 21.2, 42.4, 39.4, 45.5, 18.2, 21.2, and 18.2% in control, PS, NS, NA, UF only, PS+U, NS+U, and NA+U, respectively. Four treatments, PS, PS+U, NS+U, and NA+U, reduced the incidence of dialysis failure significantly as compared with control ($P < 0.05$) and were evaluated in the phase 2 study, a randomized controlled 6-wk crossover study. Parameters were measured in the steady state after a 6-wk maintenance of each treatment. Diffusive sodium gain (ΔNa) was significantly increased with sodium balance–positive profiles with or without UF profile, PS and PS+U (PS 1.9 ± 1.1 , PS+U 1.7 ± 1.0 mEq/L; both $P < 0.05$ to control -0.1 ± 0.2 , NS+U 0.5 ± 0.4 , NA+U 0.4 ± 0.2 mEq/L). They also increased the interdialytic weight gain (PS 3.8 ± 0.6 , PS+U 4.0 ± 0.6 kg; both $P < 0.05$ to control 2.7 ± 0.6 , NS+U 3.3 ± 0.6 kg; both $P = NS$ to NA+U 3.5 ± 0.6 kg). Predialysis weight and the required amount of UF also increased significantly with these sodium balance–positive profiles. Although the absolute amount of UF was larger with PS and PS+U, %UF achieved targeting dry weight was higher with sodium balance–neutral profiles with UF profiles, NS+U and NA+U (NS+U 92.7 ± 3.8 , NA+U $93.7 \pm 6.8\%$; both $P < 0.05$ to control 72.6 ± 14.0 , PS 88.3 ± 6.6 , PS+U $88.2 \pm 8.2\%$). Postdialysis weight was closest to dry weight with these treatments showing Δ (postdialysis weight – dry weight) of 0.3 ± 0.1 and 0.3 ± 0.2 kg in NS+U and NA+U (both $P < 0.05$ to control 1.0 ± 0.6 kg; both $P = NS$ to PS 0.5 ± 0.3 , PS+U 0.5 ± 0.4 kg). Incidence of excessive weight gain and subjective discomforts during the interdialytic period increased significantly with PS. In conclusion, continuous use of sodium balance–positive sodium profiles resulted in an undesirable steady state with sodium and fluid expansion offsetting their hemodynamic benefit. Sodium balance–neutral sodium profiles in combination with UF profile were associated with less sodium and weight gains, better UF performance with postdialysis weight closest to dry weight, and fewer interdialytic problems with the equivalent hemodynamic benefit. Therefore, it is proposed that sodium balance–neutral sodium profiling HD with UF profile is a better choice, ensuring the dialysis of quality without sodium gain–related complications.

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Intradialytic hypotension-related discomforts (IHD) are a common complication of hemodialysis (HD), with the incidence of 20 to 30% of treatments (1). It is a major hindrance and has a negative impact on health-related quality of

life in patients who are on the maintenance HD (2). Apart from patients' subjective discomforts, IHD often requires the early discontinuation of the dialysis session and/or the fluid replacement that results in chronic volume overload and underdialysis (3,4). Current guideline of the Dialysis Outcome Quality Initiative (DOQI) recommends that every effort be undertaken to minimize IHD that compromises the delivery of adequate dialysis (5).

Sodium profiling hemodialysis is a dialysis maneuver developed to avoid IHD by the modulation of dialysate sodium concentration according to preestablished profiles (e.g., chang-

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ing dialysate sodium concentration, mostly from high to low, typically from initially supraphysiologic values) (6,7). It was designed to reserve the benefits from high-dialysate sodium and avoid unnecessary intradialytic sodium gain at the same time. Nevertheless, the negative consequences by sodium gain have been frequently reported: Thirst, excessive interdialytic weight gain, dyspnea, and the development of hypertension (8–15). Independent of the detailed course of a profile, an important consideration during sodium profiling HD is the sodium balance that is determined by the intradialytic diffusive sodium transport: Positive, negative, or neutral (7,8,16). We recently reported that the time-averaged mean of dialysate sodium has a close relationship with the complication related to intradialytic diffusive sodium gain (9). However, the relevant studies are scarce on the effects of sodium balance considering both sides of sodium profile: Preventing IHD and avoiding sodium accumulation.

Ultrafiltration (UF) profile is another maneuver to prevent IHD in which UF rate is profiled to be interrupted intermittently or to be decreased stepwise or gradually to induce plasma refilling so as to prevent hypotensive episodes. When it is combined with sodium profiles, UF profile can potentiate the elevation of plasma tonicity, providing a greater driving force for plasma refilling by high UF rate during a high-sodium period. It can also avoid hypovolemia, reducing the incidence of hypotensive episodes by low UF rate during a low-sodium period (4,7,8). Therefore, the combination of UF profile has been a common practice during sodium profiling HD (4,8,17).

In the present study, we evaluated the protocols of sodium profiling HD with various sodium balances and with or without the combination of UF profile. Our analysis focused on not only preventing IHD but also maintaining the quality of dialysis and minimizing the sodium accumulation. This prospective study consisted of two steps: Screening the effective protocols in preventing IHD and evaluating them on the changes in the sodium and fluid balance. During the first step, the protocols were evaluated in terms of the effectiveness on preventing IHD and maintaining sufficient session time, Kt/V , and UF. The protocols determined as “acceptable,” as defined elsewhere, were included in the second step. The second step was a crossover study that evaluated the changes in sodium and fluid balance and the sodium gain–related complications. The parameters were measured in the steady state after 6-wk maintenance of each protocol. The patients were confined to the IHD-prone patients in the present study because they are practically the main patients who require sodium profiling HD.

The aims of the present study were to determine the optimal sodium balance of sodium profiling HD for preventing IHD and maintaining the quality of dialysis and to estimate whether such an optimal sodium profile can be carried out without sodium gain–related complications. The study also tested whether the combination of UF profile is helpful in achieving these goals. The ultimate aim of the present study was to answer the question of whether sodium profiling HD can ensure the quality of dialysis without sodium accumulation.

Materials and Methods

Patients

The study was conducted in the Inha University Hospital Outpatient Dialysis Center from May 2003 to April 2004, under the approval of the Institutional Review Board. Among 121 adult ESRD patients who underwent maintenance HD for >6 mo, we selected 17 patients who were prone to IHD under the criteria of the occurrence of IHD in >30% of the HD sessions of the previous 6 mo. Fifteen patients consented to the informed consent approved by the Institutional Review Board.

Study Design

Before the study, the patients had a 4-wk adjustment period to individualize adequate dry weight, blood flow rate, and antihypertensive regimens by the attending nephrologists. Once these parameters had been adjusted appropriately, they were strictly maintained throughout the study periods. During the phase 1 study, eight treatments that consisted of various sodium profiling protocols, with or without UF profile, were evaluated as described in Figure 1. The patients were randomly allocated to one of two sequences: Sequence 1 control→PS→NS+U→NA→UFP only→NA+U→NS→PS+U→control→PS+U→NS→NA+U→UFP only→NA→NS+U→PS→control→PS→NS+U→NA→UFP only→NA+U→NS→PS+U→control→PS+U→NS→NA+U→UFP only→NA→NS+U→PS. Five patients underwent sequence 1, and six underwent sequence 2. The study was continued until the data were obtained from total of 264 sessions with 11 patients, 33 sessions for each protocol. The treatment protocols that showed the incidence of dialysis failure, defined elsewhere as <25% of sessions, were evaluated in the phase 2 study.

Before entering the phase 2 study, the dry weight was reevaluated and readjusted if necessary by the attending nephrologists according to a method described elsewhere. The phase 2 study was a prospective crossover study that evaluated the treatment protocols that satisfactorily passed the phase 1 study. The conventional HD served as the control. It consisted of five 6-wk treatment periods: control, PS, PS+U, NS+U, and NA+U. The patients underwent the first treatment with one randomly chosen protocol among five protocols, and the next protocols were chosen one by one from among the rest of the protocols in a randomly assigned manner. Each treatment period was continued for 6 wk and separated by a 1-wk washout period with conventional HD to avoid carryover effect.

The patients were not aware of the assigned treatments throughout the study period. The attending nephrologists carried out determination of dry weight and prescription of UF amount, unaware of the assigned treatments, and did not participate in analysis. The nursing staff who undertook primary patient care proceeded with the study following the sequences as determined by randomization. These nurses carried out the intervention for IHD and recorded all of the events that occurred during the session. Another nurse was assigned only to assess interdialytic discomforts and patients' response to each treatment without information of treatment. The researchers who did not participate in the patients' treatment carried out the final analysis with the blinded data.

Dialysis Method

HD was performed using FMC 4008 H (Fresenius Medical Care AG, Bad Homburg, Germany) and polysulfone hollow-fiber dialyzer F5 or F6 (Fresenius Medical Care AG). Blood flow rate was individualized from 200 to 350 ml/min (mean 293 ± 61 ml/min) and dialysate flow

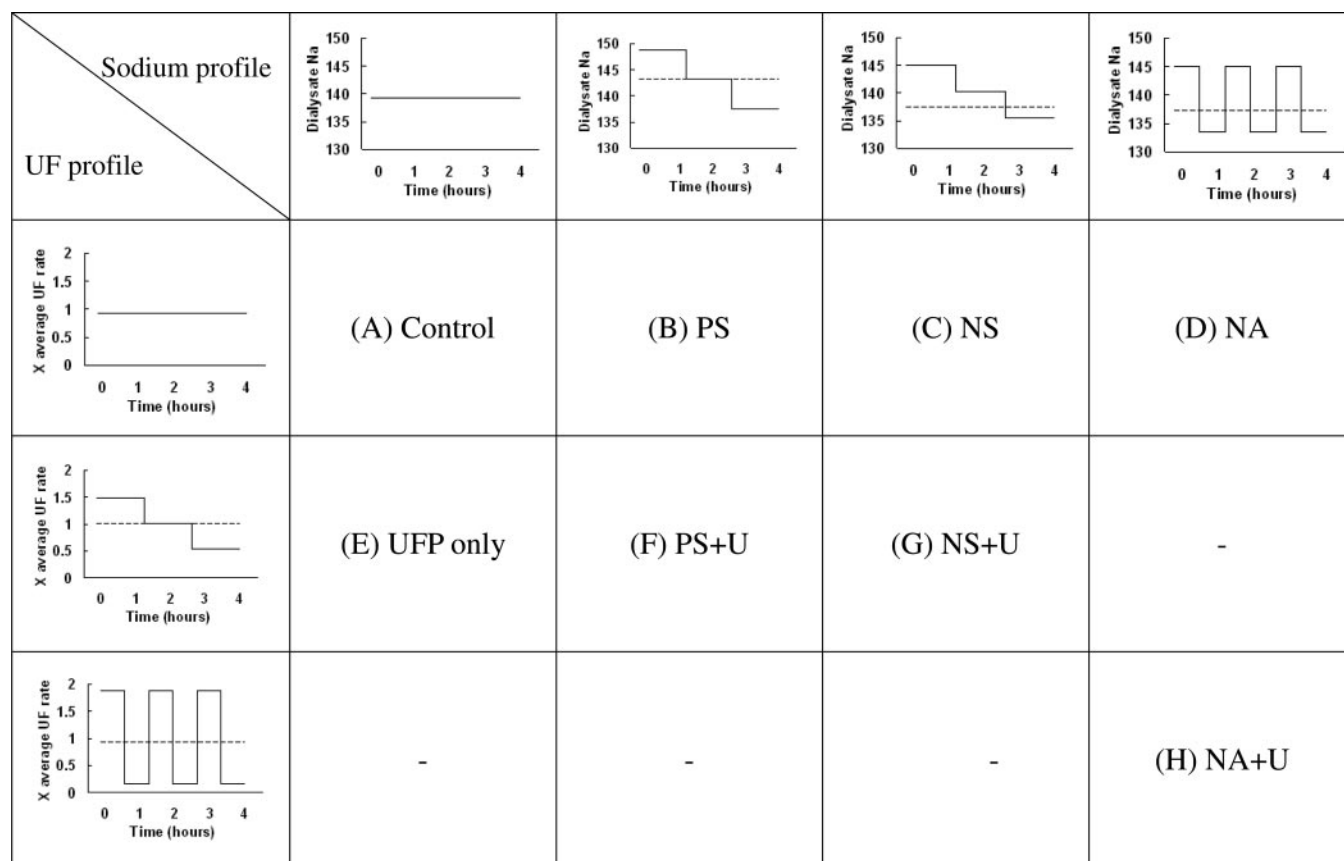


Figure 1. Treatment protocols. (A) Conventional hemodialysis (HD; control; dialysate sodium 138 mEq/L). (B) Sodium balance–positive step-down sodium profiling HD (PS; time-averaged mean of dialysate sodium 143 mEq/L). (C) Sodium balance–neutral step-down sodium profiling HD (NS; 138 mEq/L). (D) Sodium balance–neutral alternating type sodium profiling HD (NA; 138 mEq/L). (E) Conventional HD + step-down ultrafiltration profile (UFP; UFP only; 138 mEq/L). (F) PS + step-down UFP (PS+U; 143 mEq/L). (G) NS + step-down UFP (NS+U; 138 mEq/L). (H) NA + alternating type UFP (NA + U; 138 mEq/L). Dotted line, time-averaged mean of dialysate sodium or UF rate during the session.

rate was 500 ml/min. Dialysate contents were 2.5 mmol/L potassium, 1.75 mmol/L calcium, 0.75 mmol/L magnesium, 30 mmol/L bicarbonate, and 8 mmol/L acetate. Dialysate temperature was 37°C.

Sodium Profiling Method

Conventional HD was performed using the dialysate with sodium concentration of 138 mEq/L. Sodium profiling pattern, step-down or alternating, was chosen as it was programmed in the module of FMC 2008 H. The module was programmed to achieve the time-averaged mean of dialysate sodium concentration of the session automatically at the prescribed level. For the sodium balance–positive sodium profile, the prescribed sodium concentration was set at 143 mEq/L and the starting sodium concentration was set at 148 mEq/L. For the sodium balance–neutral sodium profile, the prescribed sodium concentration was set at 138 mEq/L and the starting sodium concentration was set at 145 mEq/L. Then, the module proceeded with the profile automatically while maintaining the time-averaged mean of dialysate sodium concentration at 143 mEq/L for the former and 138 mEq/L for the latter. The dialysate sodium concentrations at the final step of the step-down type and at the low-sodium period of the alternating type were automatically determined by the module to achieve desired time-averaged means, which were usually 138 to 139 mEq/L for the former and 134 to 135 mEq/L for the latter (Figure 1).

UF Profiling Method

The attending nephrologist determined the average UF rate considering both individual dry weight and interdialytic weight gain. UF profiling pattern was chosen as it was programmed in the module (Figure 1). The program automatically changed the UF rates above and below the predetermined average UF rate. In the stepwise decreasing UF profile, the UF rate began with $1.5 \times$ UF rate and decreased stepwise to $1.0 \times$ UF rate in the next step and to $0.5 \times$ UF rate in the final step. In the alternating type UF profile, there were three intervals with UF rate of $2.0 \times$ UF – 100 ml/h, interrupted by three intervals with UF rates of 100 ml/h. The durations of the six intervals were equal and were calculated from total treatment time divided by 6 (Figure 1). Stepwise decreasing UF profile was combined with step-down sodium profiles, and the alternating type UF profile was combined with the alternating sodium profile.

Estimation of Dry Weight

The patient's attending nephrologist estimated the dry weight on the basis of the finding of physical examination, plain chest x-ray, and inferior vena cava diameter (IVCD) measurement (Sonos 2500; Hewlett Packard, Palo Alto, CA). We considered the patients to be overhydrated when edema in physical examination, cardiomegaly, pulmonary con-

gestion or pleural effusion in plain chest x-ray, or IVCD >11.5 mm/m² existed (18). IVCD was defined as a mean of IVCD at inspiration and IVCD at expiration. A mean of two consequent measurements was taken.

Outcome Measurement

In the phase 1 study, clinical parameters including Kt/V, BP, UF amounts, and the incidences of noticeable events were measured for all sessions. In the phase 2 study, clinical parameters, including plasma sodium, body weights, and UF amounts, were measured for three sessions during the last week of each treatment period. The incidence of noticeable events was measured at the same time. BP was measured before and after dialysis. The minimal BP during the session was also recorded. Sodium concentration was measured from venous blood drawn directly from the nonarteriovenous fistula arm just 10 min before and after the session. It was determined on plasma sample by potentiometry using ion-selective sodium electrode (TBA-200FR; Toshiba, Tokyo, Japan), which was calibrated using the serum-based calibrator. Delivered dose was presented by Kt/V according to a natural logarithm formula: $Kt/V = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times UF/W$, where R is postdialysis blood urea nitrogen and predialysis blood urea nitrogen, t is session length in hours, UF is ultrafiltration volume in liter, and W is postdialysis weight in kg. The achievement of UF was represented in two ways according to the goal: Achieving dry weight *versus* removing the interdialytic weight gain, as follows:

% Target ultrafiltration achieved_{WG} =

$$\frac{\text{actual UF volume}}{\text{interdialytic weight gain}} \times 100 (\%)$$

% Target ultrafiltration achieved_{DW} =

$$\frac{\text{actual UF volume}}{\text{predialysis weight} - \text{dry weight}} \times 100 (\%)$$

For the evaluation of the intradialytic complications, the *session failure* was defined as the discontinuation of the session at the time before 75% of planned time. The *delivery failure* was defined as Kt/V <1.1. The *UF failure* was defined % target UF achieved_{DW} was <70%. When one or more of above occurred, we defined it as *dialysis failure*. Intradialytic discomfort was defined as the occurrence of hypotension (systolic BP <90 mmHg or a decrease >30 mmHg or an event that required immediate intervention), cramp, headache, nausea, dizziness, or fatigue. Intervention was defined as the performance of Trendelenburg position, modification of Qb or UF rate, saline infusion, or discontinuation of the session.

For the interdialytic period, objective discomforts were represented by excessive weight gain, increase of BP, and dyspnea with pulmonary edema on plain chest x-ray. Excessive weight gain was arbitrarily defined as % weight gain >7% and the increase of BP was defined as % increase of BP >10% as compared with conventional HD:

$$\% \text{ Weight gain} = \frac{\text{interdialytic weight gain}}{\text{postdialysis weight}} \times 100 (\%)$$

$$\% \text{ Increase of BP} = \frac{\text{predialysis MAP}}{\text{predialysis MAP of previous session}} \times 100 (\%)$$

The subjective discomfort during the interdialytic period was defined as the complaint of fatigue, thirst, weakness, or dyspnea without radiologic evidence. Subjective discomforts were recorded by filling out the preformed questionnaire form in Korean language by the patients under the guidance of one assigned nurse. Finally, all patients' re-

sponses to each treatment were recorded as good, same, or bad at the end of each treatment period.

Statistical Analyses

All values of continuous variables were presented as mean $\pm$ SD. Means of continuous values for each patient ($n = 11$) were used for analysis in the phase 1 and phase 2 studies. The incidences of noticeable events were expressed as numbers of episodes for all observed sessions ($n = 33$) in both phase studies. Statistical analysis was performed using SPSS for Windows release 10.0 (SPSS Inc., Chicago, IL). Paired *t* test was used to determine whether there were significant differences in the continuous variables among the protocols in the phase 1 and phase 2 studies at the 95% confidence interval. The incidences of measured events were compared using χ^2 analysis in both phase study periods. Two-tailed $P < 0.05$ was considered to be significant.

Results

Baseline Characteristics

Among 15 patients who consented to the study, four could not complete the study for the reasons not related the study protocol; two had transferred to other hospitals, one had undergone kidney transplantation, and one had died from cardiac arrest. The mean age of the patients was 54 ± 9 yr, and mean duration of HD was 37 ± 38 mo (Table 1). Mean baseline Kt/V was 1.23 ± 0.11 in the baseline. The causes of ESRD were diabetes (5 patients), chronic glomerulonephritis (4 patients), hypertension (1 patient), and unknown (1 patient).

Phase 1: Screening of Protocols

There was a trend for an increase of delivered dose of dialysis (Kt/V) with PS, PS+U, PS+U, NS+U, and NA+U but did not reach statistical significance. The incidence of delivery failure showed a similar result (Table 2). BP showed no differences among all treatment protocols except for significant increases in minimal systolic BP with PS and PS+U. The incidences of intradialytic discomforts, intervention, and session failure were decreased with PS, PS+U, NS+U, and NA+U. Statistical significance was found in PS, PS+U, and NS+U for the intradia-

Table 1. Patient baseline characteristics^a

N	11
Age (yr)	54 ± 9
Gender (F:M)	7:4
Hemodialysis duration (mo)	37 ± 38
Kt/V	1.23 ± 0.11
Estimated dry weight (kg)	49.1 ± 8.9
Hemoglobin (g/dl)	8.7 ± 1.1
Hematocrit (%)	25.9 ± 3.4
Total protein (g/dl)	6.8 ± 0.5
Albumin (g/dl)	3.4 ± 0.3
Blood urea nitrogen (mg/dl)	64.1 ± 16.2
Creatinine (mg/dl)	9.2 ± 2.6
Diabetes (%)	5 (45.5)
Left ventricular dysfunction (%)	7 (63.6)
No. of antihypertensives	2 ± 1

^aData are mean $\pm$ SD.

Table 2. Comparison of eight treatments^a

	Control	PS	NS	NA	UFP Only	PS+U	NS+U	NA+U
Kt/V	1.21 ± 0.10	1.23 ± 0.19	1.21 ± 0.17	1.21 ± 0.16	1.20 ± 0.10	1.24 ± 0.11	1.23 ± 0.12	1.23 ± 0.18
Delivery failure (%)	9 (27.3)	6 (18.2)	9 (27.3)	10 (30.3)	9 (27.3)	4 (12.1)	5 (15.2)	6 (18.2)
Systolic BP (mmHg)								
predialysis	148 ± 17	149 ± 19	149 ± 18	144 ± 16	148 ± 17	150 ± 19	148 ± 15	148 ± 20
minimal	103 ± 16	126 ± 19 ^b	107 ± 18	113 ± 17	113 ± 19	129 ± 17 ^b	121 ± 18	126 ± 18
postdialysis	126 ± 15	137 ± 20	129 ± 19	136 ± 19	136 ± 17	143 ± 16	138 ± 17	139 ± 15
Diastolic BP (mmHg)								
predialysis	85 ± 8	86 ± 10	84 ± 11	84 ± 8	83 ± 10	84 ± 10	84 ± 9	85 ± 11
minimal	60 ± 10	68 ± 11	62 ± 9	65 ± 10	61 ± 9	69 ± 11	67 ± 9	67 ± 10
postdialysis	75 ± 9	77 ± 10	76 ± 9	75 ± 10	74 ± 8	79 ± 10	78 ± 10	79 ± 9
Intradialytic discomforts (%)	18 (54.5)	7 (21.2) ^c	15 (45.5)	16 (48.5)	14 (42.4)	8 (24.2) ^c	9 (27.3) ^c	11 (33.3)
Intervention (%)	13 (39.4)	6 (18.2)	11 (33.3)	11 (33.3)	12 (36.4)	5 (15.2) ^c	6 (18.2)	7 (21.2)
Session failure (%)	9 (27.3)	4 (12.1) ^c	8 (24.2)	9 (27.3)	8 (24.2)	3 (9.1) ^c	3 (9.1) ^c	4 (12.1) ^c
%Target UF achieved _{DW} (%)	70.6 ± 9.1	89.8 ± 12.4 ^b	78.7 ± 11.0	78.9 ± 12.4	74.2 ± 11.3	89.6 ± 9.1 ^b	91.2 ± 10.9 ^b	91.0 ± 9.7 ^b
UF failure (%)	12 (36.4)	4 (12.1) ^c	8 (24.2)	11 (33.3)	12 (36.4)	3 (9.1) ^c	5 (15.2) ^c	4 (12.1) ^c

^aData are mean ± SD. Control, conventional hemodialysis; PS, sodium balance–positive step-down sodium profiling hemodialysis; NS, sodium balance–neutral step-down sodium profiling hemodialysis; NA, sodium balance–neutral alternating type sodium profiling hemodialysis; UFP only, conventional hemodialysis with step-down UF profile; PS+U, sodium balance–positive step-down sodium profiling hemodialysis with step-down UF profile; NS+U, sodium balance–neutral step-down sodium profiling hemodialysis with step-down UF profile; NA+U, sodium balance–neutral alternating type sodium profiling hemodialysis with alternating type UF profile.

^b $P < 0.05$ versus control by paired t test.

^c $P < 0.05$ versus control by χ^2 test.

lytic discomforts; in PS+U for the requirement of intervention; and in PS, PS+U, NS+U, and NA+U for the session failure. The achievement of UF targeting dry weight (%UF achievement_{DW}) increased and the incidence of UF failure decreased significantly with PS, PS+U, NS+U, and NA+U. The incidences of dialysis failure were 48.5, 21.2, 42.4, 39.4, 45.5, 18.2, 21.2, and 18.2% in the control, PS, NS, NA, UF only, PS+U, NS+U, and NA+U, respectively (Figure 2). PS, PS+U, NS+U, and NA+U reduced the incidence of the dialysis failure to <25%, showing a statistically significant difference as compared with control ($P < 0.05$). Therefore, these four treatment protocols and conventional HD as control were evaluated in the phase 2 study.

Phase 2: Plasma Sodium Concentration in the Steady State

We maintained each treatment continuously for 6 wk so as to obtain the sodium and body weight levels after reaching the steady state. Diffusive sodium gain during the session (ΔNa) was significantly increased with sodium balance–positive sodium profiling protocols regardless of the combination of UF profile (PS and PS+U) as compared with control and sodium balance–neutral sodium profiling protocols (NS+U and NA+U; Table 3, Figure 3A). Postdialysis sodium concentration was significantly increased with PS and PS+U as compared with control, NS+U, NA+U (Figure 3B). Predialysis plasma sodium concentration was also significantly increased with PS

and PS+U as compared with control, NS+U, and/or NA+U. It was highest with PS+U, which was significant as compared even with PS.

Phase 2: Body Weight and UF Parameters in the Steady State

The interdialytic weight gain was significantly increased with PS and PS+U, which were statistically significant as compared with control and NS+U (Table 3). Perhaps as a conse-

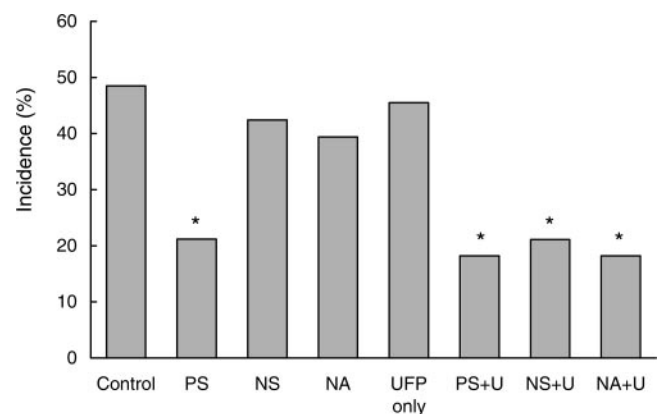


Figure 2. Incidences of the dialysis failure of treatment protocol. The dialysis failure was reduced <25% with PS+U, NS+U, and NA+U (* $P < 0.05$ versus control by χ^2 test).

Table 3. Steady-state plasma sodium concentration, body weight, and ultrafiltration parameters^a

	Control	PS	PS+U	NS+U	NA+U
Plasma sodium (mEq/L)					
predialysis	138.1 ± 0.3 ^{c,d}	138.5 ± 0.50 ^{b,d,e}	139.1 ± 0.7 ^{b,c,e,f}	138.1 ± 0.2 ^{c,d}	138.1 ± 0.7 ^d
postdialysis	138.1 ± 0.1 ^{c,d}	140.4 ± 0.4 ^{b,e,f}	140.8 ± 0.4 ^{b,e,f}	138.6 ± 0.3 ^{c,d}	138.6 ± 0.4 ^{c,d}
Δ (postdialysis – predialysis)	–0.1 ± 0.2 ^{c,d}	1.9 ± 1.1 ^{b,e,f}	1.7 ± 1.0 ^{b,e,f}	0.5 ± 0.4 ^{c,d}	0.4 ± 0.2 ^{c,d}
Body weight (kg)					
predialysis	52.8 ± 8.6 ^{c,d}	53.3 ± 8.6 ^{b,e,f}	53.6 ± 8.5 ^{b,e,f}	52.6 ± 8.6 ^{c,d}	52.8 ± 8.8 ^{c,d}
postdialysis	50.1 ± 9.0 ^{e,f}	49.7 ± 8.9	49.6 ± 8.9	49.3 ± 8.7 ^b	49.4 ± 8.8 ^b
Ultrafiltration (kg)	2.7 ± 0.6 ^{c,d,e,f}	3.6 ± 0.6 ^{b,e}	4.0 ± 0.7 ^{b,e}	3.3 ± 0.5 ^{b,c,d}	3.5 ± 0.5 ^b
Interdialytic weight gain (kg)	2.7 ± 0.6 ^{c,d,e,f}	3.8 ± 0.6 ^{b,e}	4.0 ± 0.6 ^{b,e}	3.3 ± 0.6 ^{b,c,d}	3.5 ± 0.5 ^b
%Target UF achieved _{WG}	100.9 ± 20.1	99.2 ± 6.7	101.4 ± 6.4	101.8 ± 8.1	99.0 ± 5.3
%Target UF achieved _{DW}	72.6 ± 14.0 ^{c,d,e,f}	88.3 ± 6.6 ^{b,e,f}	88.2 ± 8.2 ^{b,e,f}	92.7 ± 3.8 ^{b,c,d}	93.7 ± 6.8 ^{b,c,d}

^aData are mean ± SD.

^b*P* < 0.05 versus control by paired *t* test.

^c*P* < 0.05 versus PS by paired *t* test.

^d*P* < 0.05 versus PS+U by paired *t* test.

^e*P* < 0.05 versus NS+U by paired *t* test.

^f*P* < 0.05 versus NA+U by paired *t* test.

quence, predialysis weight and the amount of UF were significantly increased with PS and PS+U as compared with all others in the former and as compared with control and NS+U in the latter. However, postdialysis weight was reduced significantly with NS+U and NA+U as compared with control. PS and PS+U also decreased postdialysis weight, but the statistical significance was not found.

In the steady state, as shown in Figure 4A, predialysis weights were 4.3 ± 0.6 and 4.6 ± 0.6 kg excess dry weight with PS and PS+U, which were significantly higher as compared with 3.7 ± 0.5 , 3.5 ± 0.5 , and 3.8 ± 0.5 kg with control, NS+U, and NA+U, respectively. They were not different among control, NS+U, and NA+U. However, the patients completed the dialysis sessions with the postdialysis weight of 0.3 ± 0.1 and 0.3 ± 0.2 kg excess dry weight with NS+U and NA+U, which were significantly lower as compared with 1.0 ± 0.6 kg with control. They were 0.5 ± 0.3 and 0.5 ± 0.4 kg excess dry weight with PS and PS+U. In terms of removing the interdialytic weight gain, UF performance was sufficient with all treatment protocols so that %target UF achieved_{WG} was nearly 100% in all protocols. However, in terms of achieving dry weight, it revealed to be not sufficient in control and lower in sodium balance–positive sodium profiles as compared with sodium balance–neutral sodium profiles. %Target UF achieved_{DW} was significantly higher with NS+U and NA+U compared with PS and PS+U. It was significantly lower with control as compared with all other treatment protocols (Figure 4B).

Phase 2: Intra- and Interdialytic Complications and Patient Response to Sessions

The incidences of adverse events were decreased with all treatments as compared with control, which was similar to the results from the phase 1 study. The decreases in some parameters showed a statistically significant difference, but others showed only a definite trend. The dialysis failure was signifi-

cantly reduced with all profiling protocols as compared with control (Table 4). Intradialytic subjective discomforts and excessive weight gain occurred more frequently with PS. Other intradialytic complications were high with PS and PS+U but did not reach statistical significance. The patients responded positively to PS, PS+U, and NS+U. It is interesting that fewer patients scored well in NA+U.

Discussion

The present study showed that sodium balance–positive sodium profiling HD inevitably caused the excessive sodium gain when it was used continuously. As a consequence, it resulted in new steady state with sodium and volume expansion that offset its merit in preventing IHD. It ultimately increased patients' weights despite high UF performance. Conversely, sodium balance–neutral sodium profiling HD could obtain similar intradialytic hemodynamic benefit without sodium gain on the condition that UF profile was combined. It improved the sodium and volume balance so as to achieve the ideal dry weight easily. Among sodium balance–neutral sodium profiling protocols, patients seemed to be more comfortable with the step-down type than with the alternating type.

Accumulation of sodium and fluid is the predominant factor in the pathogenesis of hypertension and left ventricular hypertrophy in HD patients (1). An adequate removal of sodium and water during HD is of prime importance in improving the dismal cardiovascular risk profile of HD patients (16). Sodium profile is a maneuver designed to prevent IHD by preserving blood volume and thus increasing the tolerance to UF. Although it has been substantially reported as a useful tool to improve dialysis tolerance (6–10), an important debate still remains on the possibility of intradialytic sodium gain. The review of literature indicates that the sodium profiles with supraphysiologic sodium concentrations during most of the

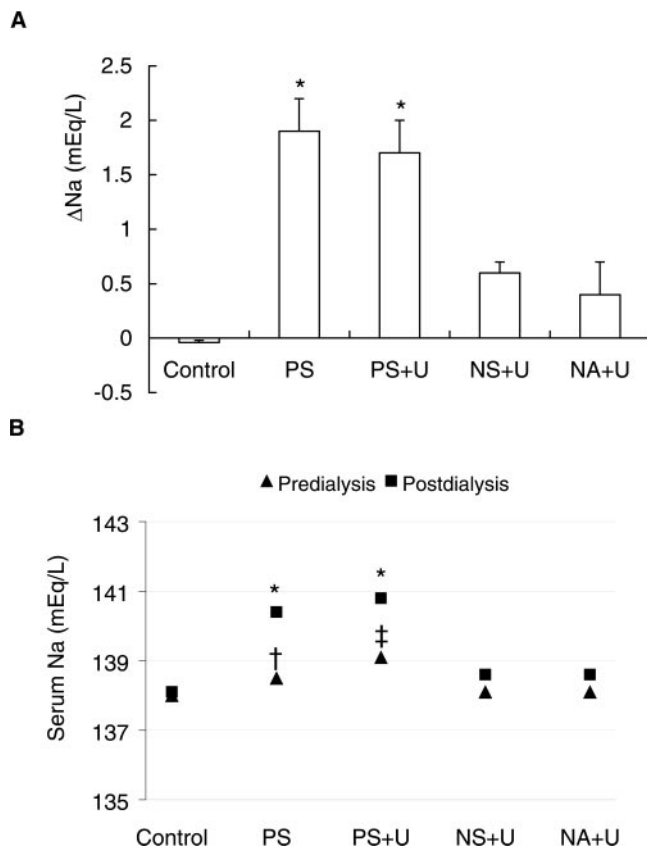


Figure 3. (A) Δ Sodium (Na) was increased significantly with PS and PS+U, suggesting that sodium balance–positive sodium profiles increased the diffusive sodium gain. (B) Sodium balance–positive sodium profiles increased the steady-state level of plasma sodium concentration not only for postdialysis but also for predialysis as compared with control and sodium balance–neutral sodium profiles. * $P < 0.05$ versus control, NS+U, and NA+U; † $P < 0.05$ versus control, PS+U, and NS+U; ‡ $P < 0.05$ versus control, PS+U, NS+U, and NA+U; error bar is omitted to avoid the complexity in B.

dialysis sessions frequently result in increased thirst and interdialytic weight gain (6–15). Flanigan *et al.* (13) and we (9) have demonstrated that the use of sodium profiling with high time-averaged dialysate sodium concentration leads to sodium gain and its related consequences. However, few data are available on the effect of sodium balance with relevant comparisons. Sodium profile may be promising, but it always has to be without sodium gain–related problems.

Sodium balance–positive sodium profile, with time-averaged dialysate sodium concentration of 143 mEq/L, showed an improvement of hemodynamic tolerance in phase 1 of the present study. However, the further detailed investigations in phase 2 revealed the negative consequences of phase 2: Increase in intradialytic sodium gain, interdialytic weight gain, and some interdialytic complications. Although sodium balance–positive HD showed a higher absolute amount of UF, we assumed that this was only the consequence of the increase in interdialytic weight gain. In the steady state, postdialysis body weights were higher with sodium balance–positive profile as compared with

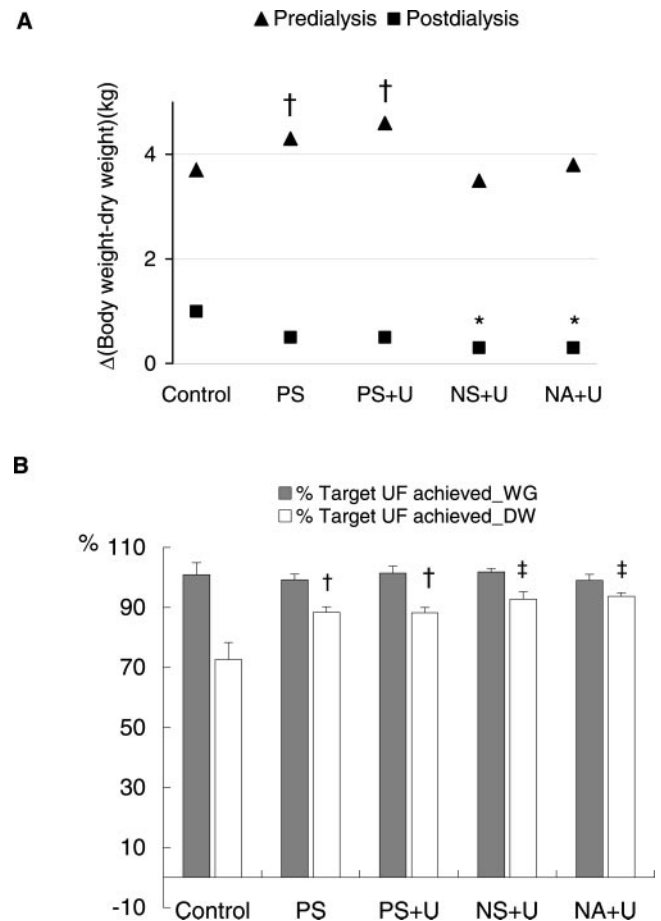


Figure 4. (A) Sodium balance–neutral sodium profiles achieved postdialysis weight closest to the dry weight with a lesser amount of UF. Lesser interdialytic weight gain with sodium balance–neutral sodium profiles might contribute to this benefit. (B) UFP to remove interdialytic weight gain (%target UF achieved_{WG}) was similarly sufficient with both sodium balance–positive and –negative sodium profiles, but the performance to achieve ideal dry weight (%target UF achieved_{DW}) was less sufficient with sodium balance–positive sodium profiles. * $P < 0.05$ versus control; † $P < 0.05$ versus control, NS+U, and NA+U; ‡ $P < 0.05$ versus control, PS, and PS+U; error bar is omitted to avoid the complexity in A.

those with sodium balance–neutral profile. Therefore, the benefits of improving hemodynamic tolerance and UF performance were offset by the increase of weight gain. It could be proposed that the continuous use of sodium balance–positive sodium profile might induce a vicious cycle of the more interdialytic weight gain and the more UF requirement resulting in the undesirable steady state of sodium and fluid balance. In terms of achieving ideal sodium and fluid balance, our results suggested that sodium balance–positive sodium profile was not an appropriate therapeutic choice.

Many authors have recently focused on sodium balance–neutral sodium profile. Because it is neutral with respect to the intradialytic diffusive sodium balance (7,8,16), it is theoretically possible that it avoids the sodium gain–associated complications while preserving hemodynamic tolerance. Despite the

Table 4. Intra- and interdialytic complications and patient responses^a

	Control	PS	PS+U	NS+U	NA+U
Intradialytic period^b					
intradialytic discomforts (%)	17 (51.5)	7 (21.2) ^d	8 (24.2) ^d	8 (24.2) ^d	10 (30.3)
intervention (%)	12 (36.4)	6 (18.2)	5 (15.2) ^d	7 (21.1)	6 (18.2)
delivery failure (%)	9 (27.3)	5 (15.2)	5 (15.2)	4 (12.1)	6 (18.2)
UF failure (%)	11 (33.3)	3 (9.1) ^d	4 (12.1)	3 (9.1) ^d	5 (15.2)
session failure (%)	8 (24.2)	3 (9.1)	2 (6.1)	3 (9.1)	4 (12.1)
dialysis failure (%)	14 (42.4)	7 (21.1) ^d	6 (18.2) ^b	6 (18.2) ^d	7 (21.1) ^d
Interdialytic period^b					
subjective discomfort (%)	6 (18.2)	15 (45.5) ^{d,e}	12 (36.4)	5 (15.2)	7 (21.2)
% weight gain >7% (%)	4 (12.1)	11 (33.3) ^{d,e}	9 (27.3)	3 (9.1)	4 (12.1)
% increase of BP >10% (%)	6 (18.2)	8 (24.2)	8 (24.2)	6 (18.2)	7 (21.2)
pulmonary edema (%)	3 (9.1)	6 (18.2)	5 (15.2)	2 (6.1)	3 (9.1)
Patient responses^c					
good	3	7 ^d	7 ^d	8 ^d	5
same	1	2	3	2	4
bad	7	2	1	1	2

^aData are mean ± SD.^bNumber of episodes (%) for 33 sessions during the last weeks of each treatment period.^cResponses from 11 patients at the end of each treatment period.^d $P < 0.05$ versus control by χ^2 test.^e $P < 0.05$ versus NS+U and NA+U by χ^2 test.

expectation, however, such benefits have not been shown convincingly (6,7,16). Some early studies reported that sodium profile with average dialysate sodium concentration of physiologic level obtained the hemodynamic benefits without sodium gain (19,20), but the benefits were too moderate to justify its use. One recent study dealing with this issue reported that, aside from prevention of sodium gain, sodium balance–neutral sodium profile failed to improve dialysis tolerance (21).

In terms of the hemodynamic benefits, sodium balance–neutral profiles in the present study might also be moderate. When the evaluation was extended to the delivery of dialysis dose, maintenance of session, and UF performance, however, the therapeutic value became substantial. When combined with UF profile, it reduced the incidence of the dialysis failure as much as the sodium balance–positive sodium profile did. The more important advantage of sodium balance–neutral sodium profile HD with UF profile in the present study was that it achieved a desirable steady state of sodium and fluid balance. They were associated with less sodium and weight gain, better UF performance with postdialysis dry weight closest to dry weight, and less interdialytic problems showing intradialytic benefit as similar as sodium balance.

There are some methodologic differences in the present study as compared with most of the previous studies. We believe it to be the positive aspect of the present study, although others may regard it as the negative aspect. First, we evaluated the benefits of the profiles not only for the incidence of IHD but also for the maintenance of dialysis session, delivered dose, and UF performance. The incorporation of these parameters was to evaluate the benefits more comprehensively in terms of maintaining the quality of dialysis. It seemed that

the obvious beneficial effect in our phase 1 study, as compared with other studies, was in part contributed by this comprehensive evaluation. Second, in the phase 2 study, the parameters were measured after continuous use of each protocol for 6 wk. This undoubtedly accentuated the sodium accumulation and its adverse effects during sodium balance–positive sodium profiles. However, by this, we could demonstrate that the continuous use of sodium balance–positive sodium profiles resulted in a new steady state with volume and sodium expansion compared with the initial level. To the best of our knowledge, this is the first study to report the consequences of the “continuous use” of sodium profiling HD. Third, we added an analysis of UF performance in terms of achieving the dry weight. In most previous studies, UF performance has been represented simply by presenting the absolute amount of UF, and, in most cases, it was determined to remove the interdialytic weight gain after the previous session. This could make it difficult to discriminate the gradual accumulation of fluid. However, our analysis method revealed that sodium balance–positive sodium profiles failed to achieve target dry weight, although their absolute amount of UF is higher as compared with others.

The patients in the present study were confined to IHD-prone patients, who are practically the main patients who require sodium profile. This patient characteristic contributed to extraordinarily low delivered dose of dialysis in the present study as compared with the usual HD population. In the phase 1 study, the complete randomization was practically impossible with eight treatment protocols. Therefore, we randomized the patients into one of two sequences in which the order of treatment was transposed. The sequences of treatment were de-

signed to avoid both order effects and carryover effects as much as possible.

The patients, the attending nephrologists dealing with dry weight and UF, and the nurse assigned to assess interdialytic events and patients' response to treatment were blinded to the assigned treatments. The only data obtained without blinding were those on intradialytic events recorded by other nursing staff. Blinding to these nursing staff was practically impossible because they should undertake direct patient care and ensure patient safety during the session. We do not believe that this would have affected the results, because they reacted only passively to the events that occurred during the session according to directions.

We do understand that there are several limitations to the present study. First, the number of the cases might not be sufficient to be statistically powered. This might have resulted in the statistically insignificant difference of some intradialytic parameters despite their definite trend of decrease. Second, the absolute value of dry weight study might not be accurate. Some of the patients have never reached the dry weight because of an undesirable hemodynamic state during the dialysis session. In such cases, we had to estimate the dry weight on the basis of the clinical findings and measurement of inferior vena cava diameter. We believed that this was not crucial for the aim of the present study because the dry weight was used just as a standard for comparing the changes in fluid balance. Third, the effect of UF profile was not fully evaluated in the present study. We evaluated only a step-down decreasing UF protocol among many other protocols, as a matter of convenience. Therefore, the effectiveness of UF profile should not be concluded with our results. For example, a continuously decreasing UF profile that showed a good performance in the previous work (17) might have shown better results.

Undoubtedly, the sodium profile with time-averaged mean dialysate sodium of 143 mEq/L tested in the present study is sodium balance positive. However, some authors would disagree with our definition of sodium balance neutral. We defined sodium balance neutral in terms of the dialysate-side sodium concentration with a rough assumption that the time-averaged mean dialysate sodium concentration of 138 mEq/L is neutral. This might be criticized because the sodium activity of the dialysate side might not be equal to that of the patient's side. True sodium balance–neutral dialysis can be defined only after confirming no change in the patient's plasma sodium concentration. This requires an additional exhaustive trial-and-error work to find the optimal dialysate sodium concentration, which is beyond the scope of the present study. When this is achieved, "isonatremic dialysis" will be a more exact and appropriate term (22). The future of sodium profile is promising as the achievement of isonatremic dialysis is currently becoming easier owing to the development of in-line conductivity monitoring and feedback control techniques (23–25).

We did not measure the total body sodium mass balance. The changes in plasma sodium concentration do not accurately reflect that of the total body sodium mass. The introduction of the single-pool sodium kinetic model permitted the calculation of total sodium mass balance (26–28). A mathematical model

was developed to calculate final plasma conductivity, that is, final plasma sodium concentration and required dialysate conductivity to achieve the target final plasma conductivity (23,28,29). Conductivity feedback system incorporating this model permits the modulation of plasma conductivity and thus isonatremic dialysis customized to the individual patient. Currently, blood volume–controlled feedback systems are also available (30–31). This system directly monitors the change in blood volume and maintains stable blood volume by adjusting the UF rate and dialysate conductivity. We believe that these technological developments will guarantee the intradialytic hemodynamic stability in the future.

In conclusion, the present study demonstrated that continuous use of a sodium balance–positive sodium profile resulted in the undesirable steady state with sodium and fluid expansion despite its hemodynamic benefit and high UF capability. Sodium balance–neutral sodium profiles combined with UF profile were associated with less sodium and weight gain, better UF performance, closer postdialysis to dry weight, and less interdialytic problems with equivalent benefits in preventing IHD and maintaining the quality of dialysis to sodium balance–positive profile. The combination of UF profile was prerequisite for these benefits. Patients were more comfortable with the step-down type than with the alternating type among sodium balance–neutral sodium profiling HD. The present study indicated that the long-term use of sodium balance–positive profiling HD should be avoided. We carefully propose that sodium balance–neutral sodium profiling HD with UF profile is a better choice, ensuring the quality of dialysis without sodium gain-related complications.

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