

Effect of Dialysate Sodium Concentration on Sodium Gradient and Hemodialysis Parameters

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This retrospective study was performed to determine the ranges of the sodium gradient (SG) between the dialysate sodium concentration (DNa) and serum sodium concentration (SNa) in hemodialysis (HD) patients and to examine the relationships between HD parameters over a 1 year period. Fifty-five clinically stable HD patients, who had been on HD >2 years were enrolled. Monthly HD [ultrafiltration (UF) amount, systolic blood pressure (SBP), frequency of intradialytic hypotension (IDH)] and laboratory data were collected and 12-month means were subjected to analysis. The SG was calculated by subtracting SNa from prescribed DNa. Mean SG values were 1.5 ± 3.3 (range -5.6~9.1). SG was positively related to DNa and the frequency of IDH. A higher SG was associated with larger UF amounts and SBP reduction during HD. The percentages of patients with a SG ≥ 3 mEq/L increased as DNa increased. On the other hand, SG was not found to be associated with SNa or pre-HD SBP. DNa appears to cause a significant increase in SG, and this seems to be related to HD parameters, such as, UF amount and IDH.

Key Words: Renal dialysis, Dialysis solutions, Sodium

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Introduction

In chronic HD patients, sodium (Na^+) balance largely depends on interdialytic dietary salt intake and intradialytic Na^+ removal¹⁾. To preserve a neutral Na^+ balance, interdialytic Na^+ gain should be removed during HD.

From the 1980s, dialysis units have adopted high sodium bicarbonate dialysate because a higher dialysate sodium concentration (DNa) reduces the level of dialysis discomfort and the incidence of symptomatic hypotension and disequilibrium²⁾. However, there is concern that a DNa higher than the serum sodium concentration (SNa) will result in a diffusive Na^+ flux from dialysate to the patient,

which can lead to a positive Na^+ balance during HD and cause fluid overload and hypertension²⁾. Indeed, higher sodium gradients (SGs) are associated with increased thirst³⁾ and interdialytic weight gain^{3,4)}.

Furthermore, dialysis patients appear to have a unique set point for $\text{SNa}^5)$, which is stable over long-term observations⁶⁾ and is actively defended⁷⁾. Therefore, the use of a fixed DNa for all HD patients can cause a positive Na^+ balance in some patients, which strengthen the importance of DNa individualization to achieve neutral Na^+ balance⁸⁾.

The aim of this retrospective study was to document sodium gradient (SG) ranges using SNa and SNa corrected for the Gibbs-Donnan effect, the void volume, and even

for hyperglycemia in HD patients, and to examine relationships between SG, ultrafiltration (UF) amount, and blood pressure (BP).

Materials and Methods

1. Subjects

This retrospective, observational, clinical study was performed on end stage renal disease (ESRD) patients who were followed up at a HD center in Inha University Hospital (Incheon, Republic of Korea) from February 2013 to January 2014. In this HD center, DNa had been previously fixed to 138 mEq/L for all patients. However, in view of associated problems, such as, volume overload and hypertension, DNa was individualized to BP from January 2010. In patients whose BP was well controlled, DNa was maintained at 138 mEq/L, but in others, DNa was reduced to 135 or 136 mEq/L. On the other hand, in patients who exhibited dialysis hypotension infrequently, DNa was increased to 140 or 142 mEq/L. In patients who exhibited dialysis hypotension frequently, a sodium profiling or combined sodium/ultrafiltration profiling method was applied.

HD patients that had been clinically stable for more than 2 years were enrolled in this study. The exclusion criteria were congestive heart failure, liver cirrhosis, malignancy, acute myocardial infarction, any hemodynamically unstable condition, the requirement for a sodium profiling method during HD, hospital admittance for infection, cardiovascular disease, malignancy, transfer to another hospital, or kidney transplantation during the study period. Of the 102 patients initially considered, 55 were considered eligible and these patients constituted the study cohort.

HD was performed for 4 hours per session, three times per week, using a polysulfone dialyzer (F6HPS, Fresenius Medical Care, Bad Homburg, Germany) and a Fresenius Medical Care 5008 machine. Dialyzers were not reused. Hemotrate[®]-B No. 1 and No. 2 (JW Pharmaceutical, Republic of Korea) were used as dialysate concentrates for non-diabetics, and Hemo B dex[®] 0.15% No. 1 and No. 2 (JW Phar-

maceutical, Republic of Korea) were used for diabetics. Blood flow rates were between 250 and 300 mL/min, depending on the arteriovenous fistula status. The dialysate flow rate was 500 mL/min. BP was measured hourly using an automated BP measuring device attached to the dialysis machine. Kt/Vurea values were calculated using the Daugirdas second generation equation¹⁰.

The study protocol was approved by the Institutional Review Board of Inha University Hospital and complied with the Declaration of Helsinki. The requirement for written consent was waived because of the retrospective nature of the study. All data used was obtained routinely for the purpose of patient management.

2. Correction of serum sodium (SNa)

Serum sodium concentrations (SNa) were measured using an indirect potentiometry method (Hitachi 7600, Toshiba, Tokyo). All SNa values were corrected for void volume and the Gibbs-Donnan effect using the following formula:

$$csNa = SNa \times [1.007 - (0.009 \times TP)] / [0.989 - (0.0047 \times TP)],$$

where TP is serum total protein (g/dL) and csNa is corrected SNa⁹.

When serum glucose exceeded 100 mg/dL, SNa was further corrected for glucose, using the following formula:

$$csNag = csNa + 0.0016 \times [\text{serum glucose} - 100],$$

where csNag means csNa corrected for serum glucose concentration¹¹.

3. Calibration of dialysate sodium concentration

The quality of DNa delivery was assured by taking monthly DNa measurements and by machine calibration.

4. Calculation of sodium gradient

The sodium gradient between dialysate and blood was calculated using the following equations:

$$SGna = DNa - SNa,$$

$$SGcna = DNa - csNa,$$

$$SGcnag = DNa - csNag,$$

where SGna is the sodium gradient calculated using

SNa, SGna the sodium gradient calculated using csNa, SGnag the sodium gradient using csNag, and DNa is the prescribed DNa.

5. HD and laboratory data

UF amount, DNa, pre- and post-HD SBP, and dry weight data were determined at monthly blood examinations, and biochemical data, that is, pre-HD SNa, glucose, total protein (TP), albumin, BUN, creatinine, hemoglobin, and post-HD BUN were obtained from the medical records from February 2013 to January 2014. Serum osmolality was calculated using the following equation:

$$sOsm (mOsm/kg) = 2 \times SNa + BUN/2.8 + \text{glucose}/18,$$

where sOsm is the calculated serum osmolality¹². Δ SBP was calculated as follows:

$$\Delta SBP = (\text{pre-HD} - \text{post-HD}) \text{ SBP}.$$

The 12-month means of the variables for each patient were analyzed. The number of intradialytic hypotension (IDH) episodes was also investigated. The definition of IDH used was a modification of that used by Chesterton et al., that is an SBP of <100 mmHg with or without symptoms¹³.

6. Statistical analysis

Results are presented as means \pm SDs or as medians, modes and ranges. The coefficient of variation (CV) of SNa was calculated using the following equation:

$$CV = SD \times 100 / \text{mean}$$

Differences between SNa and csNa or csNag were evaluated using a paired t-test. The unpaired Student's t-test was used to determine the significance of differences between group mean values. Group categorical data were compared using the chi-square test, and the Pearson's correlation coefficients were used to determine the natures of relationships between two variables. P-values of <0.05 were considered significant.

Results

1. Patient characteristics

Of 55 patients, 26 (47.3%) were male and 24 (43.6%)

were diabetics (Table 1). Mean overall patient age was 59 \pm 11 years, mean patient dry weight was 67 \pm 10 kg, and mean HD duration was 8.5 \pm 4.4 years. The mean number of anti-hypertensive drugs being taken was 1.6 \pm 1.2. At study commencement, mean pre-HD BUN, creatinine, hemoglobin, total protein, albumin, glucose concentrations, and Kt/Vurea were 79.3 \pm 18.7 mg/dL, 11.4 \pm 2.8 mg/dL, 10.3 \pm 1.1 g/dL, 6.9 \pm 0.4 g/dL, 4.0 \pm 0.3 g/dL, 144 \pm 67 mg/dL, and 1.4 \pm 0.2, respectively.

2. Analysis of sodium gradient-related data

In the 55 patients, SNa values ranged from 130 to 142 mEq/L and the mean CV of SNa was 1.5 \pm 0.5%. The numbers of patients with a SNa between 130 and 137 mEq/L, 138 and 139 mEq/L, and 140 and 144 mEq/L were 29 (52.7%), 19 (34.5%), and 7 (12.7%), respectively, and mean SNa, csNa and csNag were 137 \pm 3, 136 \pm 3, and 137 \pm 2 mEq/L, respectively (Fig. 1A, 1B, 1C). Mean SNa was significantly higher than the mean csNa and csNag ($p < 0.01$). On Bland-Altman plots, csNa was \sim 1.6 mEq/L lower than SNa (Figs. 2A and 2B), and csNag was 0.8 mEq/L lower than SNa but had a wider distribution than csNa.

The mean DNa values of 28 (50.9%), 13 (23.6%), 7 (12.7%), 6 (10.9%), and 1 (1.8%) patient were 138, 142, 136, 140, and 135 mEq/L respectively, and mean SGna,

Table 1. Patient characteristics

Characteristics	Value
N	55
Male (N, %)	27 (47.3)
Diabetics (N, %)	24 (43.6)
Age (years)	59 \pm 11
Body weight (kg)	67 \pm 10
HD duration (years)	8.5 \pm 4.4
BUN (mg/dL)	79.3 \pm 18.7
Creatinine (mg/dL)	11.4 \pm 2.8
Hb (g/dL)	10.3 \pm 1.1
Total protein (g/dL)	6.9 \pm 0.4
Albumin (g/dL)	4.0 \pm 0.3
Kt/Vurea	1.4 \pm 0.2
SNa (mEq/L)	137 \pm 3

HD: hemodialysis, BUN: blood urea nitrogen, Hb: hemoglobin, SNa: serum sodium concentration

SGna, and SGcnag values were 1.5 ± 3.3 (range $-5.6 \sim 9.1$, median 0.8, mode -0.3), 3.0 ± 3.3 (range $-4.0 \sim 10.4$, median 2.5, mode -4.0), and 2.2 ± 3.1 (range $-4.4 \sim 10.4$, median 2.0, mode -4.4) mEq/L, respectively.

Significant positive correlations were observed between DNa and SGna ($r=0.60$, $p<0.01$), SGcna ($r=0.59$, $p<0.01$), or SGcnag ($r=0.58$, $p<0.01$). In addition, significant positive correlations were noted between mean UF amounts and SGna ($r=0.40$, $p=0.002$, Fig. 3), SGcna ($r=0.40$, $p=0.003$), or SGcnag ($r=0.44$, $p=0.001$), and between mean Δ SBP and SGna ($r=0.34$, $p=0.012$, Fig. 4), SGcna ($r=0.35$, $p=0.009$), or SGcnag ($r=0.31$, $p=0.02$). On the other hand, no relationship was observed between

pre-HD mean serum osmolality and SGna, SGcna or SGcnag, or between pre-HD SBP and SGna, SGcna or SGcnag. In addition, no correlation was found between DNa and mean SNa, csNa, or csNag values.

The patients were allocated to group 1 (SGna, SGcna or SGcnag <3 mEq/L) and group 2 (SGna, SGcna or SGcnag ≥ 3 mEq/L). Using SGna or SGcnag, the number of group 2 was zero when DNa was 135 or 136 mEq/L. On the other hand, group 2 patients showed from DNa 138 mEq/L and percentages increased when DNa was increased to 140 and 142 mEq/L (10.7, 50.0, and 69.2% in SGna, 17.9, 66.7, and 69.2% in SGcnag) (Fig. 5). Group 2 patients even showed from DNa 136 mEq/L

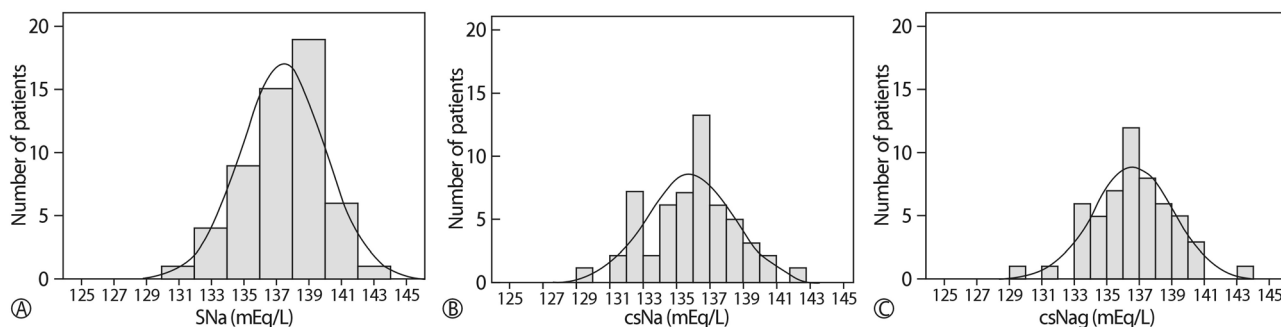


Fig. 1. Distribution of the mean (A) SNa, (B) csNa, and (C) csNag values of the study subjects.

SNa: serum sodium concentration, csNa: SNa corrected for void volume and the Gibbs-Donnan effect, csNag: csNa corrected for glucose concentration.

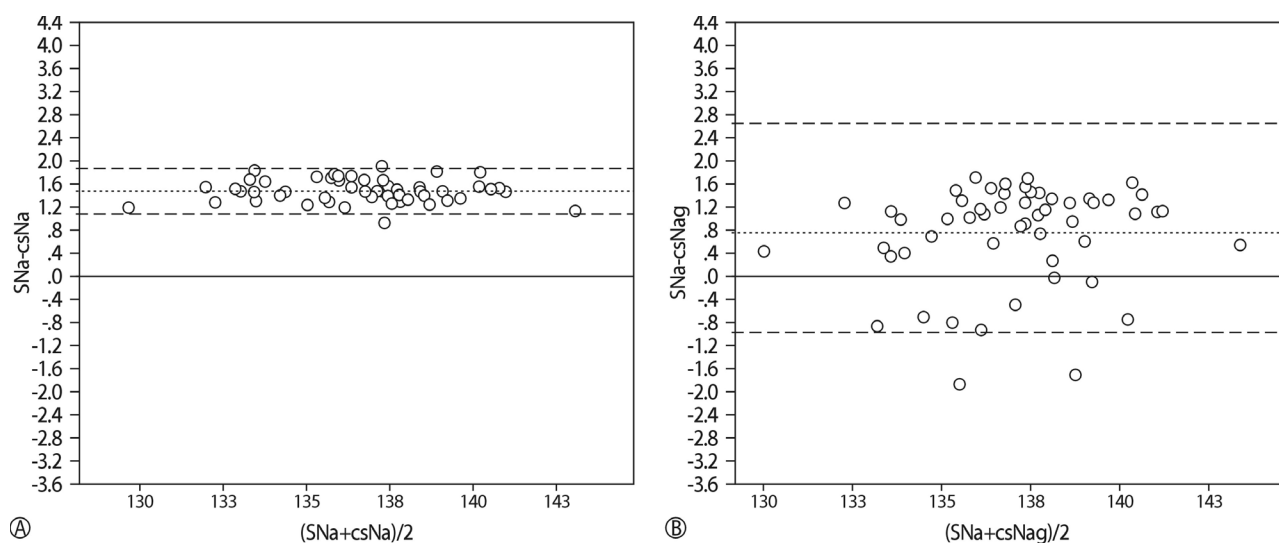


Fig. 2. Bland-Altman plot between (A) SNa and csNa, and between (B) SNa and csNag. SNa: serum sodium concentration, csNa: SNa corrected for void volume and the Gibbs-Donnan effect, csNag: csNa corrected for glucose concentration.

when SGcna (28.6% in 136 mEq/L, 17.9% in 138 mEq/L, 66.7% in 140 mEq/L, and 76.9% in 142 mEq/L) was used. Group 2 had significantly lower pre-HD SNa, csNa, csNag, serum osmolality levels and higher mean UF amount than group 1 for all 3 SG values (Table 2). Group 2 also contained more diabetics than group 1.

3. Relationship between sodium gradient and intradialytic hypotension

During the yearlong study period, 17 patients experienced IDH; 1 episode in 7 patients, 2 in 4 patients, 3 in

4 patients, 8 in one patient, and 9 in one patient. 38 patients (69.1%) did not experience IDH. Significant correlations were found between the frequency of IDH and DNa ($r=0.358, p=0.007$) (Fig. 6), mean SNa ($r=-0.34, p=0.011$), and SGna ($r=-0.34, p=0.011$). Frequency of IDH increased as SG increased, regardless of SGna, SGcna, or SGcnag. Furthermore, IDH occurred even when the SG was zero.

Discussion

This study confirms the presence of a patient specific distribution of pre-HD SNa among study subjects. In addition,

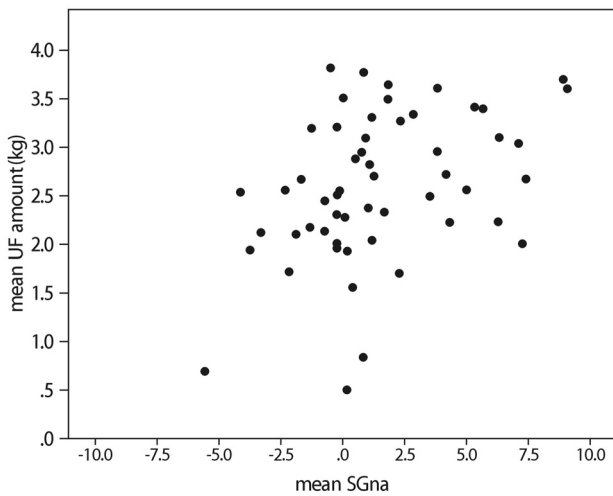


Fig. 3. Correlation between mean SGna and mean ultrafiltration (UF) amount ($r=0.40, p=0.002$).

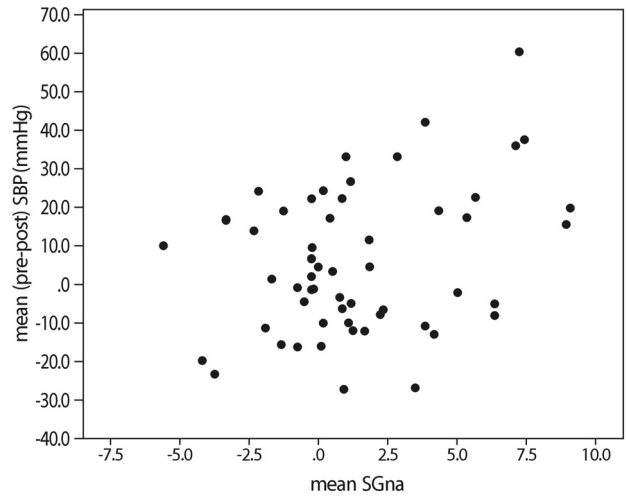


Fig. 4. Correlation between mean SGna and mean (pre - post) SBP ($r=0.34, p=0.012$). Δ SBP: (pre - post) SBP.

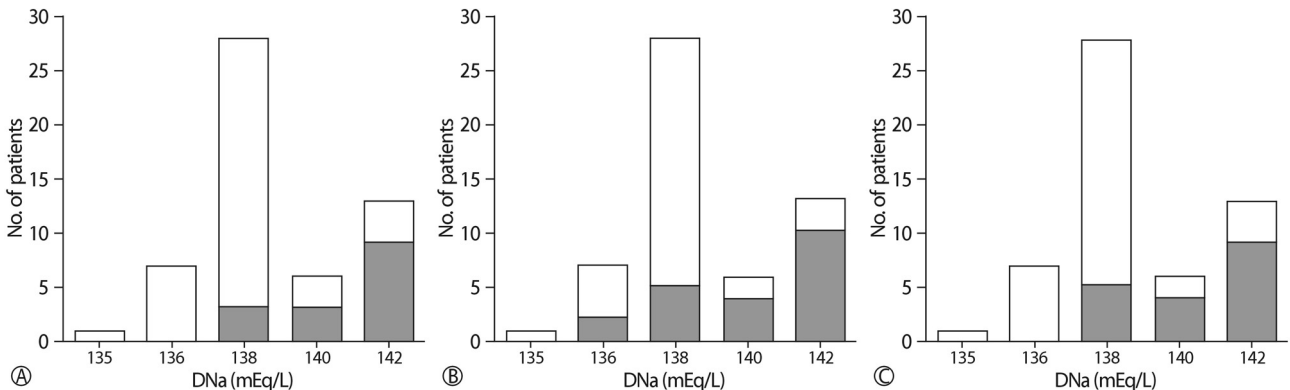


Fig. 5. Number of patients (filled squares) of (A) SGna, (B) SGcna, and (C) SGcnag ≥ 3 mEq/L among total patients (white squares) according to DNa concentration.

Table 2. Comparison between group 1 (SG <3 mEq/L) and 2 (SG ≥3 mEq/L)

	SGna		p-value
	Group 1 (<3 mEq/L) (n=40)	Group 2 (≥3 mEq/L) (n=15)	
DM (N, %)	14 (35.0)	10 (66.7)	0.065
SNa (mEq/L)	138±2	135±2	<0.01
csNa (mEq/L)	137±2	134±2	<0.01
csNag (mEq/L)	137±2	135±2	<0.01
UF (L/session)	2.49±0.80	2.93±0.56	0.056
Osmolality (mOsm/kg)	309.8±5.5	305.3±8.8	0.029
Pre-HD SBP (mmHg)	154±16	148±20	0.232
Numbers of anti-hypertensive drugs	1.8±1.1	1.1±1.2	0.05
ΔSBP (mmHg)	2.4±15.7	13.5±24.2	0.114

All values are 1-year means, SNa=serum Na, csNa=SNa, corrected for void volume and Gibbs-Donnan efficient, csNag=corrected for hyperglycemia, ΔSBP=(pre - post) HD SBP

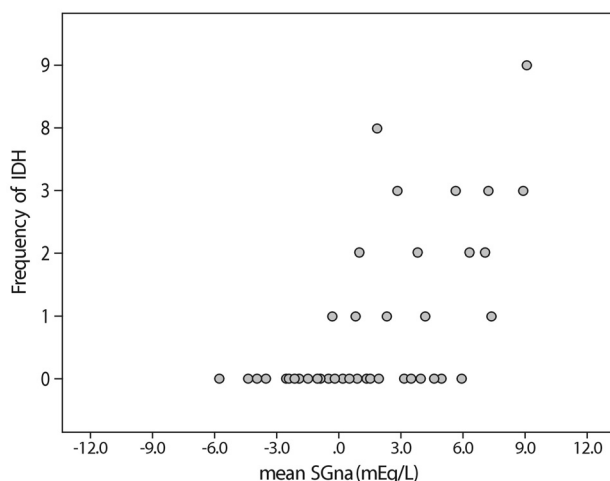


Fig. 6. Correlation between the frequency of intradialytic hypotension (IDH) and mean SGna ($r=0.358$, $p=0.007$).

tion, csNa and csNag were significantly lower than SNa, and SG was found to be positively related to DNa and the frequency of IDH. Moreover, a higher SG was associated with a larger amount of UF and a reduction in SBP during HD. In particular, patients with a SGna of more than 3 mEq/L tended to have a DNa of ≥138 mEq/L and the percentages of these patients were increased as DNa was increased. On the other hand, SG did not appear to be associated with SNa or pre-HD SBP.

Several DNa have been used for HD, but the optimal concentration remains controversial. Dialysis units generally used a high DNa, because it reduces dialysis discom-

fort and the incidences of symptomatic hypotension and disequilibrium²). However, when a high DNa is used, the increased SG produced could result in a cumulative total body Na⁺ expansion, excessive thirst, increased interdialytic weight gain, and the recrudescence of hypertension in sensitive individuals⁵). Indeed, a high DNa has been associated with increased thirst³) and interdialytic weight gain^{3,4}). Accordingly, our results are in line with those of previous reports. In addition, we observed positive correlations between DNa and SG, and between SG and UF amount (which reflects interdialytic weight gain). On the other hand, the correlation between SG and Pre-HD SBP was not consistent. Several studies have concluded SG and high DNa are not associated with pre-HD hypertension^{3,14}). Similarly, in the present study, no correlation was observed between SG and pre-HD SBP. Interestingly, numbers of anti-hypertensive drugs tended to be less in patients with a SGna of >3, which might have been due in part to the adjustment of DNa according to BP status.

Dialysis patients appear to have a unique set point for SNa⁵), that remains stable over long-term observations⁶), and which is actively controlled⁷), and our results concur with this observation. We found SNa varied with a mean CV of $1.5 \pm 0.5\%$ over the one year study period.

Therefore, the optimal of DNa appears to be patient and SG dependent¹⁵). Several studies have focused on sodium alignment, which effectively reduces interdialytic

weight gain, anti-hypertensive drug requirements, and intradialytic morbidity^{9,16,17}. However, the application of Na⁺ alignment presents several problems, such as, the feasibility of measuring SNa prior to each HD session, the need to correct for the Gibbs-Donnan effect, void volume, and hyperglycemia, the methods used to measure SNa, and the accuracy of the DNa delivered by the dialysis machine on a prescribed DNa setting⁹. Raimann et al. presented a straightforward means of correcting for the Gibbs-Donnan effect and void volume⁹, and there is a well known means of correcting SNa for hyperglycemia^{11,18}. When we compared SNa with csNa and csNag, we found it was significantly higher than both. On the other hand, the difference between SNa and csNag was less than that of SNa and csNa. Considering that many patients visit dialysis centers after they eat a meal, it appears to be reasonable to correct SNa for void volume, the Gibbs-Donnan effect, and hyperglycemia for all patients. Therefore, csNag can be estimated by subtracting the mean difference between SNa and csNag from SNa. However, our results should be interpreted carefully and further confirmatory studies are needed.

A positive SG of ≥ 3 mEq/L has been reported to be associated with increased hospitalization and mortality¹⁹, and thus, this value was used as a cut-off value for SG. Patients with a SGna or SGcnag of ≥ 3 mEq/L showed from a DNa of 138 mEq/L. When SGcna was used, patients with a SGna or SGcnag of ≥ 3 mEq/L showed even from a DNa of 136 mEq/L. Furthermore, IDH occurred at a SG of zero, regardless of SGna, SGcna, or SGcnag. This result was surprising because, in most patients, a DNa between 138 and 142 mEq/L is considered to be the standard in current clinical practice²⁰.

These results raise the question 'If an individualized DNa prescription cannot be fulfilled in a facility, should the fixed DNa be lowered to below 138 mEq/L?' This is a hot topic in the hemodialysis field. Some specialists have recommended the use of a fixed DNa of ~ 137 mEq/L²¹, whereas others have suggested it is reasonable to prescribe a DNa between 138 and 142 mEq/L in most patients²⁰. However, they also recommended that it is

important to consider whether a given patient is within a specific clinical subset, in which there is clear evidence that a positive Na balance may benefit from the manipulation of DNa²⁰. Another group even recommended reducing the DNa to 134-138 mEq/L²². Kim et al. reported that when DNa was lower than the pre-HD SNa, pre-HD SBP and interdialytic weight gain were reduced²³. On the other hand, recent studies failed to show a decrease in mortality risk in those exposed to a lower DNa at any SNa level²⁴. An association between a low DNa and increased mortality has also been reported^{25,26}. However, due to the retrospective, observational nature of our study, it is not possible to suggest an optimal DNa.

This study had several limitations. First, active Na⁺ concentration was not measured by direct potentiometry. On the other hand, SNa is usually measured by indirect potentiometry in clinical practice. Second, the simple equation proposed by Gotch et al.²⁷ was used to correct for void volume and the Gibbs-Donnan effect, but this equation does not consider the lipid concentrations as part of the void volume. Third, this retrospective study was conducted on a small number of subjects at a single HD center. Fourth, we used prescribed DNa and DNa values were not measured directly, although we should add that HD machines were calibrated monthly.

In summary, a high SG appeared to be developed by a considerable number of patients. This appears to be because HD patients show various distributions of pre-HD SNa and SG seems to be positively related to prescribed DNa. Furthermore, SG appears to be related to UF amount, Δ SBP, and frequency of IDH. However, additional studies are needed to confirm these relations.

Conflicts of Interest

The authors have no potential conflicts of interests to declare.

Statement: This study was the subject of an oral presentation at the 34th Annual Spring meeting of Korean Society of Nephrology.

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