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Combined Clinical Consequences of an Individualized Dialysate Sodium Prescription and Dietary Sodium Restriction in Hemodialysis Patients

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Abstract

Background: The degree to which the dialysate prescription and, in particular, the dialysate sodium concentration influences blood pressure and interdialytic weight gain (IDWG) via changes in sodium flux, plasma volume or the other parameters is not well understood. The aim of the study was to investigate whether dialysis patients will have some beneficial effects of dialysate sodium set up lower than serum sodium. *Material and Methods:* Fifty patients (38 men and 12 women) underwent 20 consecutive hemodialysis (HD) sessions (8 weeks) with dialysate sodium concentration set up on 139 mmol/L (standard sodium – first phase), followed by 20 sessions (second phase) wherein dialysate sodium was set up according to individualized sodium. Variables of interest were: systolic, diastolic blood pressure, IDWG, thirst score – (Dialysis Thirst Inventory (DTI)) and complications (occurrence of hypotension and muscle cramps). *Results*: Sodium individualization resulted in significantly lower blood pressure (BP =-11.6/-3.5 mm Hg, $P < 0.001$ for systolic BP and BP = -2/-6.46 mm hg [$P = 0.194$] for diastolic BP) and IDWG (+, 2.8 ± 0.75 kg; individualized Na+ 2.2 ± 0.61 kg; $P < 0.001$). Thirst score was not significantly lower in patients with individualized-sodium than compared to standard Na group. There were no significant changes in terms of complications such as hypotension. *Conclusion*: Individualized sodium resulted in clinical benefits in normotensive and hypertensive patients.

Keywords: Interdialytic weight gain (IDWG); Hemodialysis (HD); Dialysis Thirst Inventory (DTI).

Aim of the Study

Primary: To study the effect of Individualized dialysate sodium on IDWG and blood pressure.

Secondary: To study the effect of Individualized dialysate sodium on hypotension and thrist score.

Method

Inclusion Criteria

All patients on HD for at least three months were enrolled from our dialysis unit .Patients who were receiving thrice weekly or twice weekly HD with volumetric dialysis machines (Fresenius, gambro) using bicarbonate-based dialysate and polysulfone dialyzer were selected. Patients were in stable clinical condition, stable prescribed dry weight, and residual daily urine output<500 ml/day.

Exclusion Criteria

Patients not willing to participate, severe ischemia cardiac disease with poor Left ventricular reserves were excluded.

Study Design

This was a prospective, nonrandomized, single-blind, crossover trial. The study was performed in two different phases, with each subject used as his/her own control. Dry weight, dialysis prescription, and medications were not modified during the entire study except for the dialysate sodium concentration.

In the first phase, patients underwent twenty consecutive HD sessions with a standard dialysis prescription of blood flow ≥ 300 mL/min and dialysate flow of 500 mL/min. The standard dialysate composition were as follows : bicarbonate 33 mEq/L, potassium 2.0 mEq/L, calcium 3.5 mEq/L, magnesium 1.0 mEq/L, chloride 109.5 mEq/L, and acetate 3.0 mEq/L. The dialysate sodium concentration was fixed at 139 mEq/L, which is the standard concentration used in our dialysis facility. The pre HD plasma sodium concentration was determined for each patient in three different dialysis sessions. Dialysate conductivity (13.7 ± 0.2 ms/cm) will be used as reference for dialysate sodium concentration.

In the second phase of the study, patients were again subjected to twenty consecutive HD sessions, but the dialysate Na+ concentration was set to the mean of the pre-HD Na+ concentration multiplied by the Donnan coefficient of 0.95 (individualized Na+). Sodium intake was assessed by our dietician by dietary recall method.

Clinical Parameters for the Study

Blood Pressure Measurement

Pre-, intra-, and post-HD BP will be measured using a mercury sphygmomanometer. Auscultatory measurements followed standard clinical guidelines using Korotkoff I and V sounds to indicate systolic and diastolic BP, respectively.

Dry Weight Assessment

Estimated dry weight was determined through standard clinical criteria. Ultrafiltration (UF) and IDWG will be determined based on changes in body weight before and after each HD session (UF), or between the end of HD and return to the next session (IDWG).

Dialysis-Related Hypotension and Symptoms

Dialysis-related hypotension and symptoms (headache, cramps, nausea, and vomiting) were recorded and analyzed as the number of occurrences during each study phase. Hypotensive episodes were defined as rapid changes in BP (within 15 minutes) accompanied by symptoms requiring nursing interventions, or a brisk fall in BP >40 mm Hg systolic or >20 mm Hg diastolic within a 15-minute period regardless of symptoms or interventions.

Interdialytic Thirst Scores

Interdialytic thirst scores (nil, mild, moderate, and severe) was obtained by a written questionnaire answered by the patients after each phase of the study.

Statistical Analysis

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, **Assumptions:** 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent. Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale with in each group. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis.

Results

Of a total of 50 patients , 38 (76%) were males and 12 (24%) were females(fig.2). The mean age was 51.14± 15.3 years **(Figure 1)** and subjects were on dialysis for a median time of 24 months (range 3 to 120months). Diabetic nephropathy and ischemic nephropathy was the presumed cause of the end-stage renal disease in 35 patients (70%), chronic glomerulonephritis in six (22%), tubulointerstitial disease in one (1%), and unknown in one patient (1%). Thirty-eight patients (75%) were receiving erythropoietin (5000 ± 3200 U/wk) with mean hematocrit of 31 ± 5%. The average duration of each HD session was 4.1 ± 0.3 hours. Forty-eight out of fifty patients had a mean predialysis plasma sodium concentration adjusted by the Gibbs-Donnan factor lower than the standard dialysate sodium concentration.

Predialysis plasma Na+ was similar in both periods of the study **(Figure 3)**. The coefficient of variation of pre-HD sodium concentration was 0.5% and 0.7% in the standard and individualized phases, respectively. There was a significant decrease in IDWG , UF **(Table 1 & 2)**.There were significant differences in pre- and post-HD blood pressure levels for the group taken as a whole (Table 3).Systolic BP during the individualized Na+ phase (BP= -11.6/-3.5 mm Hg, $P < 0.001$ for systolic BP and $P = 0.194$ for diastolic BP= -2.1/6.4 mm hg). Forty-eight patients (96%) were taking antihypertensive medications (mean 2.1 ± 0.6 drugs; range 1 to 4 drugs).

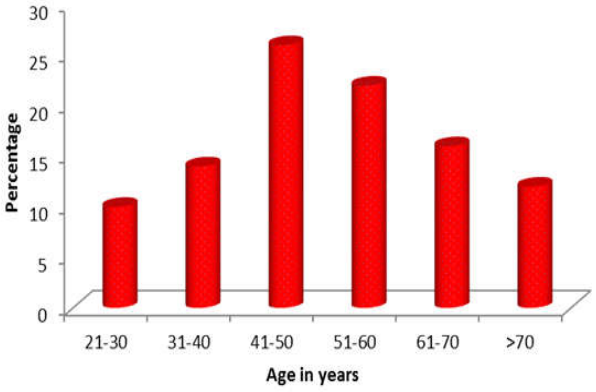

Fig. 1: Age distribution of the patients

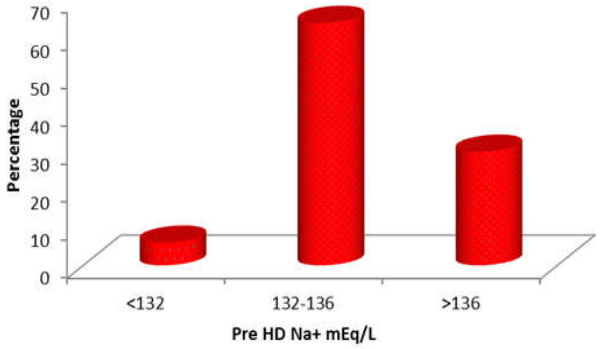

Fig. 2: Gender distribution of the patients

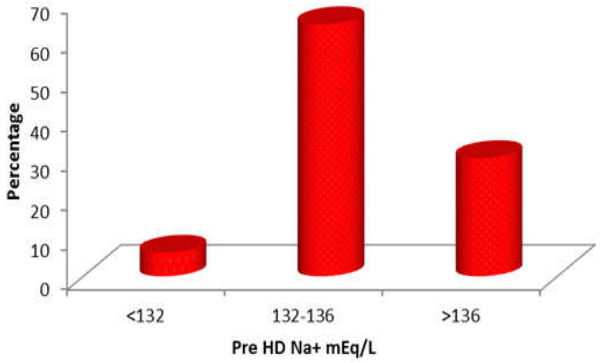

Fig. 3: Pre HD Na+ distribution in the patients

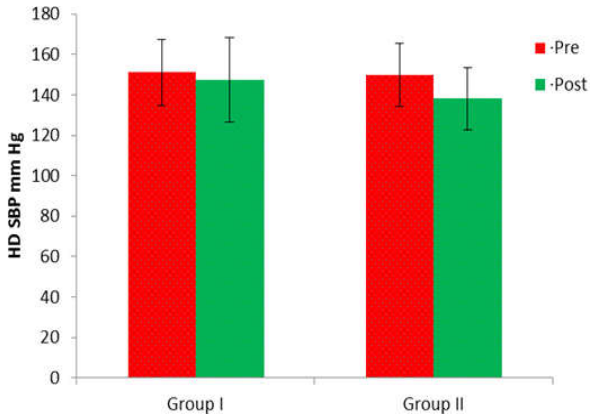

Fig. 4: Showing SBP and DBP distribution in the patients

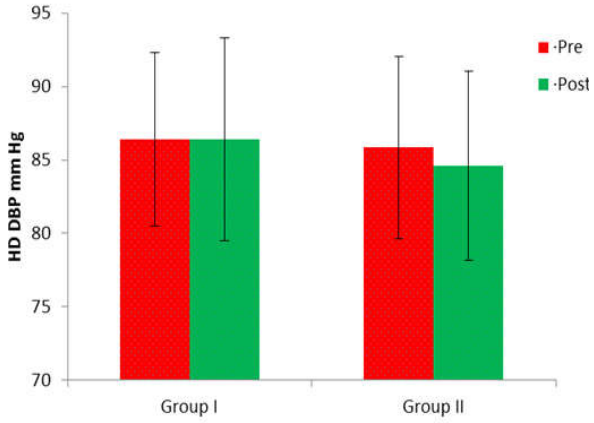

Fig. 5: Showing hypotension in both the groups.

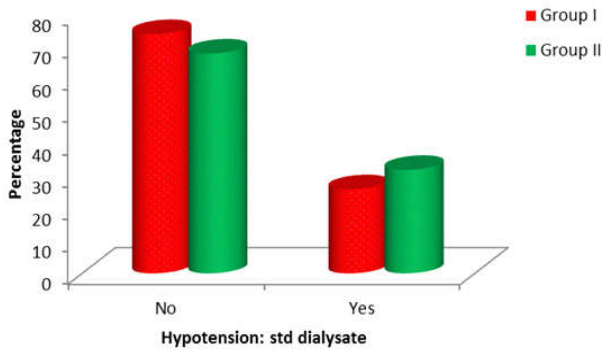

Fig. 6: Number of anti-hypertensive medications

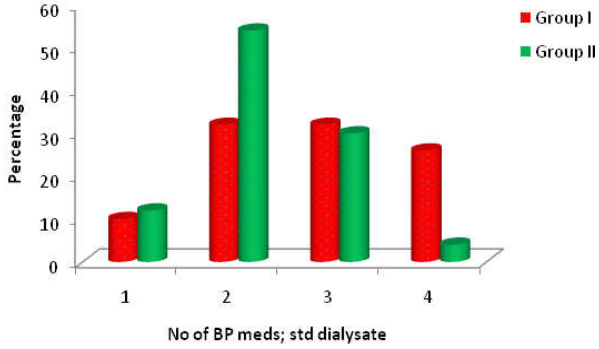

Fig. 7: Interdialytic thirst scores

No differences in achieved weight were noted between groups. Significant changes in IDWG occurred in patients with standard Na+, 2.8 ± 0.75 kg; individualized Na+ 2.2 ± 0.61 kg;($P < 0.001$). Dialysis-related hypotension and related symptoms were similar as in the individualized sodium phase of the study .Thirst scores were also similar in both the groups. Average salt consumption was 3-6 gm/ day in both groups. Even after dietary counseling , salt intake could not be reduced in the individualized Na+ phase. Number of anti-hypertensive medications were significantly reduced in the individualized Na+ phase .The maximum benefit was seen in those patients who were taking 3-4 anti-hypertensive medications which were reduced to 2-3 (P=0.012) .

Table 1: IDWG kg distribution of patients studied

IDWG kg	Group 1	%	Group 2	%
1-2	19	38	25	50
3-5	17	34	15	30
6-10	13	26	10	20
>10	1	2	0	0
Total	50	100	50	100

Table 2: Ultrafiltration of patients studied

Weight gain	Group 1	%	Group 2	%
<3	22	44	28	56
3-6	25	50	22	44
>6	3	6	0	0
Total	50	100	50	100

Table 3: Showing SBP and DBP distribution in the patients

Pre	Group I	Group II	Difference	P value
HD SBP mm Hg				
Pre	151.00±16.10	149.60±15.64	1.400	0.593
Post	147.40±20.68	138.00±15.25	9.400	0.001**
Difference	3.60	11.60	-	-
P value	0.226	<0.001**	-	-
HD DBP mm Hg				
Pre	86.40±5.92	85.84±6.21	0.560	0.654
Post	86.40±6.93	84.60±6.46	1.800	0.107
Difference	0.00	1.24	-	-
P value	1.000	0.194	-	-

P=0.509, Not significant, Chi-square test

Table 4: Hypotension: STD dialysate in group I and Group II

Hypotension: std dialysate	Group I		Group II	
	No	%	No	%
No	37	74.0	34	68.0
Yes	13	26.0	16	32.0
Total	50	100.0	50	100.0

P=0.012*, significant, Fisher Exact test

Table 5: Number of anti-hypertensive medications

No of BP meds; std Dialysate	Group I		Group II	
	No	%	No	%
1	5	10.0	6	12.0
2	16	32.0	27	54.0
3	16	32.0	15	30.0
4	13	26.0	2	4.0
Total	50	100.0	50	100.0

P=0.469, Not significant, Chi-square test

Table 6: Interdialytic thirst scores

Interdialytic thirst scores: STD dialysate	Group I		Group II	
	No	%	No	%
Nil	24	48.0	23	46.0
Mild	16	32.0	12	24.0
Moderate	10	20.0	15	30.0
Severe	0	0.0	0	0.0
Total	50	100.0	50	100.0

P=0.469, Not significant, Chi-square test

Discussion

In this study we analyzed the short-term outcome of an individualized dialysate Na+ prescription in a population of both diabetic and nondiabetic, stable HD patients. The short-term duration permitted us to leave unchanged important parameters, such as estimated dry weight, and thereby link the observed differences exclusively to the dialysate sodium changes. The main findings of our study were a reduction in IDWG, ultrafiltration, interdialytic thirst, and an improvement in predialysis BP and reduction in number of antihypertensive medications. The most prescribed antihypertensive drugs were: angiotensin receptor blockers , calcium channel blockers and β-blockers.

The Gibbs-Donnan effect in hemodialysis occurs because plasma proteins, which are negatively charged and not diffusible through the dialysis membrane, create an electric field that attracts sodium, reducing the plasma diffusible sodium by 4% to 5% [1]. As it imitates what happens in HD, we applied a theoretical Gibbs-Donnan effect of 0.95 to plasma Na+ concentration to better estimate the actual gradient between dialysate and plasma. Other methods may be used to establish the actual pre-HD dialysate to plasma sodium gradient. Dialysate conductivity reflects ionic activity and mirrors dialysate Na+ concentration when multiplied by 10 [2]. On-line dialysate and plasma conductivity can be measured inHD patients and reflects diffusible particles, mainly sodium. In machines equipped with conductivity monitors, this technique may be used to estimate the dialysate to pre- HD plasma sodium gradient, and has the advantage of allowing adjustments and matching during the dialysis session [3].

Our results showed that predialysis sodium concentration was constant when the dialysate was set to a standard concentration, and remained at the same level when the dialysate sodium concentration was individualized. This is in agreement with previous studies showing that the predialysis sodium concentration is constant independently of the sodium gradient established between blood and dialysate in the previous session [4]. This "set point" dictates the interdialytic fluid intake to bring one's osmolality back to its set point; if the post-HD Na+ is higher, greater IDWG will inevitably occur. Our data substantiate this assertion. Bylinear regression analyses, Keen and Gotch and Mendoza et all. showed a statistically significant association between the magnitude of the Na+ gradient and interdialytic weight gain and blood pressurein smaller samples of HD patients [5,6]. But, Heckinget all, reported that higher dialysate-Na prescriptions are associated with increased IDWG, but not with a higher risk for hospitalization or death. Instead, patients dialyzed with higher dialysate-Na concentrations had a significantly lower risk for hospitalization and, in facilities where all or almost all patients used the same dialysate-Na, a significantly lower risk for death [12]. Individualizing the dialysate-sodium is a simple complementary strategy to restrict sodium in HD that may help reduce IDWG in some patients [8,9].

We found a significant correlation of reducing the dialysate Na+ and IDWG in the indivialzed dialysate Na+ phase of the study. These data are in agreement with the findings of Levin et al [10], who found the same significant correlation between the dialysate to blood Na+ gradient and the absolute interdialytic weight gain.

Paula et. al [11] showed that a part of the interdialytic fluid ingestion is destined to supply the free water deficit generated by the higher dialysate sodium concentration. Our study also showed that there was significant reduction in interdialytic thirst scores, IDWG, and, concomitantly, in ultrafiltration requirements in individualized Na+ group . The decrease in the rate of fluid removal during the HD session is the most likely cause of the observed reduction in the HD hypotension episodes.

Individualization of dialysate-Na was very well tolerated by patients, probably as a result of the lower IDWG and lower UF rate, with almost few adverse events. But, on the other hand, aiming to reach eunatremia may increase the risk of intradialytic hypotension. Indeed, two studies reported a

reduction in the frequency of intradialytic hypotension after decreasing dialysate sodium [11,12]. Therefore, individualization of dialysate sodium mainly influences the IDWG and leads to better BP control in patients with poorly controlled BP and this group of patients is generally asymptomatic. On the other hand, this is not the case with hemodynamically stable patients or hypotensive-prone patients, where individualization of dialysate sodium has no influence on BP.

The main concern with the method of individualized dialysate Na+ prescription is that, in attempting to reach an isonatric HD, it could result in hyponatremia and hyposmolality-related complications because of the lack of sodium diffusion and the concomitant sodium losses by ultrafiltration. Indeed, postdialysis Na+ plasma concentration was significantly reduced in the individualized Na+ HD. However, convective sodium losses are lower than expected in HD, and were partially compensated by the reduction in the ultrafiltration and were well tolerated.

Besides, predialysis sodium remained unchanged despite the decrease in IDWG, probably related to a decrease in interdialytic fluid ingestion. Therefore, we hypothesize that the adjustment in the sodium prescription based on predialysis values may be used safely.

It could be anticipated that decreased IDWG and a more negative Na+ balance could lead to better BP control; however, it is well known that there is a lag period between changes in Na+ balance and volume status and achievement of BP control [13], we found that BP control improved after only 2-3 weeks of intervention. Several previous studies have addressed this issue in different ways [14, 15-17]. Flanigan et al and Song et al have demonstrated that the use of Na+ profiling with high time-averaged dialysate Na+ leads to higher BP carefully documented by ambulatory BP monitoring [15, 16]. Alternatively, Krautzig et al [14] and Ferraboli showed that lowering the dialysate sodium concentration to 135 mEq/L can be a successful intervention to improve BP control, a finding that was not corroborated by Kooman et al [17].

Analyses of BP data showed that, subjects had a significant overall improvement in BP control. Similar findings were reported by Flanigan et al in their study of different sodium modeling approaches, where hypertensive patients had a usual fall in BP, especially those who were not under pharmacologic treatment [15]. Presence or absence of drug treatment did not alter our results; only the presence of uncontrolled BP was a predictor of a BP-lowering response to individualized dialysate Na+ in our study

It does not seem that our results were caused by the observed changes in IDWG, as there were no significant changes in achieved weight, and hypertensive patients had a significant decrease in IDWG in the individualized Na+ HD. Individualized dialysate prescriptions lead to a decrease in ionic mass transfer to the patient [2], so it is possible that the individualized prescription led to a more favorable sodium balance and lower peripheral resistance, as has been suggested in patients undergoing daily nocturnal hemodialysis [18,19].

Our study has several limitations. 1) we did not use ambulatory BP monitoring, which is a more precise method to estimate BP in dialysis patients, as established by our own group [27]. While this is a limitation, the careful protocol observed in the determination of peridialysis BPs makes our results as reproducible as possible. 2) Free water deficit was not calculated. 3) Dialysate and post dialysis serum sodium was not evaluated.

Conflict of Interest: None

This study was conducted at ISNSC, Pondicherry 2017 for Tanker award presentation.

Conclusion

An individualized dialysate Na+ concentration was associated with a decrease in interdialytic thirst, IDWG, dialysis hypotension and related-symptoms, and better BP control in stable chronic HD patients. Long-term studies are necessary to observe if these short-term benefits are sustained.

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