

## Effects of Individualized Dialysate Sodium in Hemodialysis

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### ABSTRACT

Sodium is the major extracellular cation in the body and hence and is the major determinant of extracellular fluid (ECF) content and serum osmolarity. Volume overload contributed by increased sodium is a major problem in patients on hemodialysis (HD). Sodium entry occurs in hemodialysis patients from dietary intake, dialysis fluid or from saline infusions given during the hemodialysis session. Currently, all patients undergoing maintenance hemodialysis in our centre and hospitals world-wide are dialysed with dialysate sodium of 138 meq/L and this dialysate sodium level used as a standard value in all patients irrespective of their blood sodium values. Patients undergoing dialysis have an individualized sodium and osmolarity value which are known as sodium and osmolar set point. respectively, and are unique for each patient and is highly conserved.

A higher dialysate sodium concentration more than the patient's plasma sodium level will cause sodium gain during dialysis and increase the total body sodium. This promotes interdialytic fluid ingestion in order to restore an individual's sodium and osmolar set point. These patients might be actually having a lower sodium set point and if so, with each hemodialysis session, more sodium is continuously being added to their body, contributing to increased thirst, interdialytic weight gain (IDWG) and blood pressure. Long standing fluid overload can lead to uncontrolled hypertension, left ventricular hypertrophy and thus, lead to cardiovascular morbidity and mortality.

Theoretically, it looks advantageous to use tailor made dialysate sodium to avoid addition of excess sodium to the body during hemodialysis sessions. Several studies have been done regarding the individualization of sodium prescription in HD patients, but the results have been inconsistent. There are very few studies from India regarding sodium set points in our HD population and by prescribing Individualized dialysate sodium prescription, co-morbidities mentioned above will be drastically reduced. Our aim was to investigate and study the beneficial effects of individualized sodium profiling on patients undergoing dialysis.

**Key words:** Hemodialysis, Serum osmolarity, Hypertension, Dialysis

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### INTRODUCTION

Sodium is the major extracellular cation in the body and hence and is the major determinant of extracellular fluid (ECF) content and serum osmolarity [1]. Volume overload contributed by increased sodium is a major problem in patients on hemodialysis (HD). Sodium entry occurs in hemodialysis patients from dietary intake, dialysis fluid or from saline infusions given during the hemodialysis session. Currently, all patients undergoing maintenance hemodialysis in our centre and hospitals world-wide are dialysed with dialysate sodium of 138 meq/l [2]

and this dialysate sodium level used as a standard value in all patients irrespective of their blood sodium values. Patients undergoing dialysis have an individualized sodium and osmolarity value which are known as sodium and osmolar set point [3,4]. respectively, and are unique for each patient and is highly conserved.

A higher dialysate sodium concentration more than the patient's plasma sodium level will cause sodium gain during dialysis and increase the total body sodium. This promotes interdialytic fluid ingestion to restore an individual's sodium and osmolar set point. These patients might be actually having a lower sodium set point and if so, with each hemodialysis session, more sodium is continuously being added to their body, contributing to increased thirst, interdialytic weight gain (IDWG) and blood pressure. Long

standing fluid overload can lead to uncontrolled hypertension, left ventricular hypertrophy and thus, lead to cardiovascular morbidity and mortality.

Theoretically, it looks advantageous to use tailor made dialysate sodium to avoid addition of excess sodium to the body during hemodialysis sessions. Several studies have been done regarding the individualization of sodium prescription in HD patients, but the results have been inconsistent. There are very few studies from India regarding sodium set points in our HD population and by prescribing Individualized dialysate sodium prescription, co-morbidities mentioned above will be drastically reduced. Our aim was to investigate and study the beneficial effects of individualized sodium profiling on patients undergoing dialysis.

#### MATERIALS AND METHODS

In this prospective study, Ethical approval was obtained from Institutional research ethical committee of Sri Ramachandra Medical College and Research Institute. The study's purpose and process were explained to subjects in full prior to their participation. The participants autonomously decided whether to participate and signed the "informed consent" based on their decisions. The total sample size was 50 patients (N=50) visiting Sri Ramachandra medical centre of Sri Ramachandra University, Chennai diagnosed with end stage renal disease (ESRD) on maintenance hemodialysis, for at least 6 weeks with IDWG more than 3kg were enrolled based on following inclusion and exclusion criteria.

#### INCLUSION CRITERIA

Patients on maintenance hemodialysis with IDWG >3kg.

Duration of HD for at least 6 weeks.

Age >18yrs.

#### EXCLUSION CRITERIA

Expected life expectancy less than 6 months.

Pre-HD sodium <130meq/L or >140meq/L at recruitment.

Considered by the treating nephrologist to have concomitant illnesses or condition that limit or contraindicate study procedures and follow-

up (e.g., frequent intra-dialytic hypotension requiring fluid resuscitation).

Documented infiltrative cardiomyopathies, (amyloid, glycogen storage disease), Hereditary cardiomyopathies (hypertrophic cardiomyopathy) or moderate to severe aortic valve disease (aortic stenosis, regurgitation).

Amputees.

Failure to give informed consent.

The study was performed in two different phases, with each subject used as his/her own control. In the first phase, patients were subjected to 12 consecutive HD sessions with a standard dialysate sodium concentration fixed at 138mEq/L (standard concentration used in our dialysis unit). The pre and post-HD plasma sodium concentration were determined for each patient once a week. In the second phase of the study, patients were subjected again to 12 consecutive HD sessions with dialysate sodium concentration set to individualized value (mean of pre-HD sodium concentration multiplied by Donnan coefficient of 0.95). Difference in pre- and post-HD sodium values, intradialytic adverse events (headache, cramps, nausea, vomiting, hypotension/hypertension, requirement of nursing interventions) during both phases were assessed. All statistical analyses were performed in SPSS for Windows 20.0 (SPSS Inc., Chicago, IL, USA). These results were tabulated and presented as mean (range). P values less than 0.05 were considered as statistically significant.

#### RESULTS

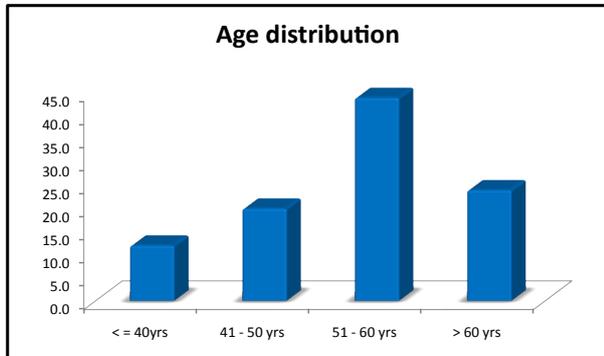
In our study, 50 patients who met the inclusion criteria were enrolled with informed consent. There were 34(68%) males and 16(32%) females with mean Age of 53.60 years (Range: 30-73years) (Table 1 and Figure 1) (Table 2 and Figure 2). Mean duration of HD in our Study was 24.60 months (Range: 6-120months). Most common cause Of ESRD in our study was Diabetic Nephropathy (54%), other causes Include Chronic Glomerular Nephritis (44%) and Chronic Interstitial Nephritis (2%). Mean Duration of HD in our study was 24.60 months ranging from 6 to 120 months.

#### Sodium levels

Dialysate sodium in standard phase (Phase I) was kept constant at 138meq/L, whereas mean

**Table 1: Age distribution of the patients (N=50).**

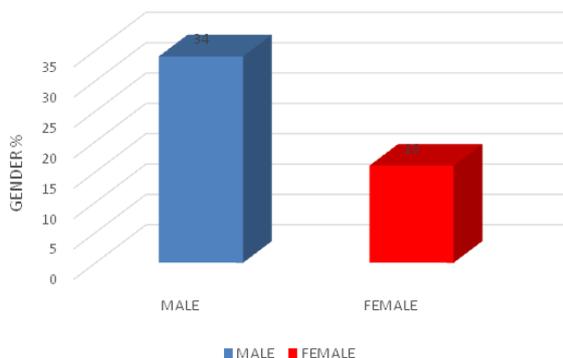
| Age in Years | No. of Patients |
|--------------|-----------------|
| <=40         | 6 (12%)         |
| 41-50        | 10(20%)         |
| 51-60        | 22(44%)         |
| >60          | 12 (24%)        |
| Total        | 50 (100%)       |



**Figure 1: Age distribution of the patients (N=50).**

**Table 2: Distribution of gender among the population group (N=50).**

| Sex    | No. of Patients |
|--------|-----------------|
| Male   | 34(68%)         |
| Female | 16 (32%)        |
| Total  | 50 (100%)       |



**Figure 2: Distribution of gender among the population group (N=50).**

dialysate sodium in individualized sodium Phase (Phase II), calculated by multiplying mean pre-HD sodium by 0.95(Donnan coefficient), was 128meq/l (Range: 124-132meq/L).

We observed a statistically significant correlation of pre- and post-HD serum sodium level between Phase I and Phase II with p value of <0.01. The mean serum pre-HD sodium level in Phase I (standard Sodium Phase) was 135.24 meq/L (Range: 131-139meq/L) and post-HD was 137.70meq/L (Range: 134-144meq/L) respectively (P<0.01)

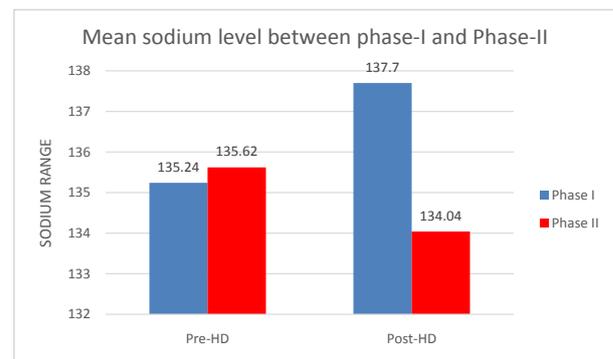
Mean dialysate sodium level in Phase II was 128meq/L (Range: 124-132meq/L). However,

in Phase-II (Individualized sodium Phase), the serum pre-HD sodium level was 135.62meq/l (Range: 131-139meq/l) while post-HD was 134.04 (Range: 130-138meq/l) respectively, which correlate statistically (P value <0.01) (Table 3 and Figure 3).

There was significant reduction in IDWG by 0.6kg in Phase II and there is also significant reduction in UF requirement by 0.5kg in individualized sodium phase (Phase II) when compared with standard phase (Phase I). On observing IDWG, Phase I was 4.050kg (Range: 3.0–6.0kg) while in Phase II, it was 3.426kg (Range: 2.5–4.1kg). There was a significant difference between the IDWG between the two phases (p<0.01). The ultrafiltration rate was drastically reduced from Phase-I which had a mean Ultrafiltration rate (UF) of 3.812kg (Range: 3.0–4.5kg) compared to phase-II which was 3.374kg (Range: 2.5–4.0kg) (Table 4 and Figure 4).

**Table 3: Pre-and Post-HD sodium distribution.**

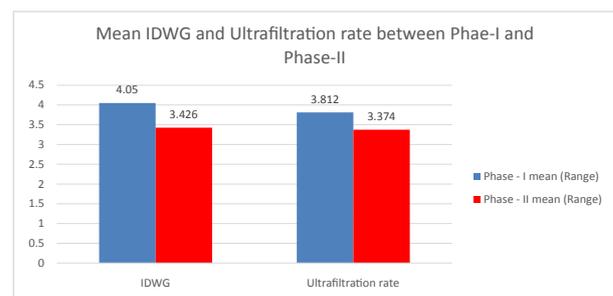
| Sodium  | Phase I | Phase II | P Value |
|---------|---------|----------|---------|
| Pre-HD  | 135.24  | 135.62   | 0.0001  |
| Post-HD | 137.7   | 134.04   | 0.0001  |



**Figure 3: Pre-and Post-HD sodium distribution.**

**Table 4: Mean IDWG and ultrafiltration rate between phase-I and Phase-II.**

| Parameter            | Phase I mean (range) | Phase II Mean (range) | P Value |
|----------------------|----------------------|-----------------------|---------|
| IDWG                 | 4.050 (3.2-6.0)      | 3.426 (2.5-4.1)       | 0.0001  |
| Ultrafiltration rate | 3.812 (3.0-4.5)      | 3.374 (2.5-4.0)       | 0.0001  |



**Figure 4: Mean IDWG and ultrafiltration rate between phase-I and Phase-II.**

### Systolic blood pressure in Phase-I

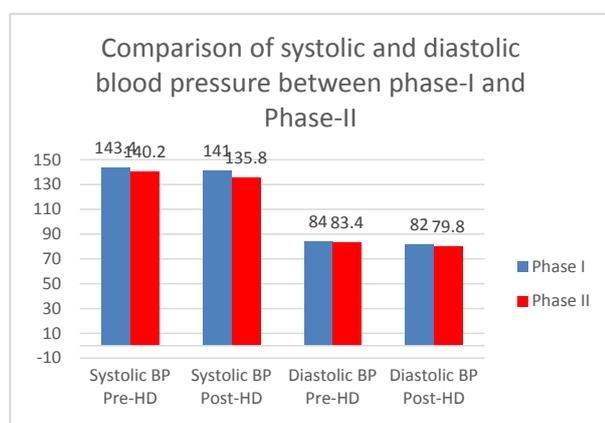
There was no significant change in the Systolic blood pressure in Phase-I pre-HD (SBP) recorded was 143.40mmHg (100 – 180mmHg), which was reduced to post HD SBP 141.0 mmHg (Range: 110–170mmHg) in the post-HD SBP (P value >0.444). However, in Phase-II, Systolic Blood pressure in Phase-II, the mean pre-HD Systolic Blood Pressure (SBP) was 140.20mmHg (100–170mmHg) and post-HD SBP was 135.80mmHg (Range: 110–160mmHg) There was statistically significance of pre- and post-HD Systolic Blood Pressure (SBP) between Phase I and Phase II (p value= 0.029).

There was statistically significant correlation of post-HD Diastolic Blood Pressure (DBP) between Phase I and Phase II with P value of 0.006(<0.01), However, the diastolic blood pressure between phase I and II was insignificant (p value = 0.444) (Table 5 and Figure 5). Mean pre-HD Diastolic Blood Pressure (DBP) in Phase II was 83.4mmHg (60 – 90mmHg) and Post-HD DBP 79.8mmHg (Range: 70–90mmHg) which correlate statistically with p value=0.008(<0.05).

The symptoms of Intradialytic complication were significantly reduced in the individualized phase. Out of 50 patients, 23(46%) patients had intradialytic complications in Phase I and only 11(22%) patients had intradialytic complications

**Table 5: Comparison of Systolic and Diastolic blood pressure between phase I and II.**

| Sodium               | Phase I | Phase II | P Value |
|----------------------|---------|----------|---------|
| Systolic BP Pre-HD   | 143.4   | 140.2    | 0.001   |
| Systolic BP Post-HD  | 141     | 135.8    | 0.001   |
| Diastolic BP Pre-HD  | 84      | 83.4     | 0.444   |
| Diastolic BP Post-HD | 82      | 79.8     | 0.006   |



**Figure 5: Comparison of Systolic and Diastolic blood pressure between phase I and II.**

in Phase II. Hypertension was significantly reduced in Phase II, Hypertension was present in 5(10%) patients, Pulmonary Oedema in 4(8%) and Hypotension in 2(4%). Compares to phase-I and was present in 11(22%) patients, Pulmonary Oedema in 9(18%) and Hypotension in 3(6%).

### DISCUSSION

Salt and water retention play a vital role in the management of intracellular and extracellular volume in the morbidity and mortality experienced by patients undergoing HD therapy. 80-90% of patients with hypertension have chronic increase in blood volume. Sodium is the predominant determinant of serum osmolarity, intracellular-intravascular fluid distribution, cell volume and blood pressure. It has been frequently observed that HD patients have a constant predialysis plasma sodium concentration, and an individualized osmolar set point. Addition of extra sodium to the body increases the volume load thereby leading to increased thirst thus increasing fluid intake to maintain the sodium and osmolar set points.

Dialysate sodium prescriptions has been driven by technological advances to improve the tolerability of the HD procedure over the past years. More emphasis has been placed on efficiency and safe delivery of therapy to large populations. As a result, dialysate composition has become relatively standardized across health care facilities.

Flanigan showed that over the duration of a year, dialysis patients have a relatively constant sodium set point which varies from 132 to 144meq/L in different patients and when these patients were dialyzed with 140meq/L dialysate sodium, their pre-dialysis to post-dialysis sodium levels had increased by 2.3–3.6meq/L [5]. Since the body attempts to maintain the sodium set point, even if water is removed during dialysis, these patients tend to drink more water during interdialytic period causing excess weight gain, increased ECF volumes and thus, higher blood pressures and its related complications.

In our study, we found that the mean pre-HD sodium level was almost similar in both the Phases, but there was a 3meq/L difference in the post-HD sodium Level in standard and individualized phases. Dialysate sodium in standard phase (Phase I) was kept constant At

138meq/L, whereas mean dialysate sodium in individualized Sodium Phase (Phase II) was calculated by multiplying mean pre-HD Sodium by 0.95 (Donnan coefficient), was 128meq/l (Range: 124-132meq/L) Gibbs-Donnan effect in hemodialysis occur due to non-diffusible, negatively charged plasma proteins creating an electric field that attracts sodium, thus reducing the diffusion of sodium from plasma across the dialysis membrane. The patients had a mean pre-HD sodium level of 135.24meq/L in the standard Phase (Phase I). This finding agreed with the study done by Radhakrishnan et al found similar results in the 40. patients where individual dialysate sodium was given and found the mean sodium content to be reduced in post-HD patients [6].

Numerous studies have shown that dialysate sodium prescriptions, individualized to each patient's sodium set point could prove beneficial. In an observational study with a facility level decrease in dialysate sodium from 141mmol/L to 138mmol/L. Thein et al in 2007 found no difference in IDWG but recorded a decrease in pre-and post-dialysis systolic and diastolic blood pressure and pre-dialysis plasma sodium [7]. This was on contrast to our study, where there was a significant reduction in IDWG by 0.6kg in Phase II along with a significant reduction in UF requirement by 0.5kg in Individualized sodium phase (Phase II) when compared with standard Phase (Phase I). This was also in agreement with the findings of the study done by Aramreddy et al. who reported on a case series of 13 patients undergoing thrice-weekly in-center hemodialysis with an individualized dialysate sodium prescription in whom dialysate sodium concentration was 2meq/L lower than average plasma sodium over the preceding 3 months. They found that individualized reduction of dialysate sodium reduces IDWG without significantly increasing frequency of cramps or hypotension [8]. Similar results have been obtained by Elshahawy et al. who studied 40 stable chronic HD patients in a single-blinded crossover design. Individualized dialysate sodium concentration was associated with a decrease in IDWG and dialysis hypotension and related symptoms and better BP control in stable chronic HD patients [9].

De Paula et al. in 2007 prospectively studied

27 hemodialysis patients and found that there was decrease in IDWG, UF rate, interdialytic thirst scores and even episodes of intradialytic hypotension in individualized sodium phase compared with the standard phase [10]. Our findings was in agreement with above mentioned study where there was a significant difference in IDWG in patients with individualized sodium intake and Ultrafiltration rate.

Our results show a significant reduction of pre-and post-HD systolic blood pressure by 3mmHg and 6mmHg respectively in individualized sodium phase (Phase II) when compared with standard phase (Phase I). There was significant reduction in post-HD diastolic blood pressure as well .by 3mmHg in individualized sodium phase (Phase II) when compared with standard phase (Phase I). However, we did not record any significant differences in pre-HD Diastolic Blood Pressure between standard phase (Phase I) and individualized sodium phase (Phase II). This was in concurrence with findings of Lambie et al. who. modified dialysate conductivity in 16 patients, progressively trying to lower dialysate conductivity from 13.6 to 13.0 mS/cm and recorded a drop in the pre-HD BP by 7/5 mmHg for both systolic and diastolic BP), an effect that was accompanied by more effective diffusive sodium removal [11].

Sayarlioglu et al. also used the predialysis sodium of 18 patients as a reference to set the dialysate sodium concentration. For those patients who had pre-HD sodium less than 137 mEq/l, the dialysate sodium was modified to 135 mEq/l, and for those with pre-HD sodium over 137 mEq/l, the dialysate sodium was modified to 137 mEq/L. After 8 weeks, reducing dialysate sodium resulted in a significant decrease in pre-HD SBP [12]. Eftimovska-Otovic et al. and Ferraboli R et al. has showed significant drop in the systolic blood pressure. In patients with individualized dialysate sodium prescription [13,14].

In the present study, there was significant reduction in number of dialysis related complications between standard and individualized phases. There was no increase in hypotension or cramps in individualized sodium phase (Phase II) despite the low sodium concentrations used during dialysis.

When plasma osmolality rapidly drops during

HD, water from the plasma is transported into the hyperosmolar intracellular compartment, leading to intravascular hypovolemia. This decline in plasma osmolality suppresses vasopressin release and promotes prostaglandin E2 secretion, impairing vasoconstriction and reduces the vascular tone [15]. When using dialysate with sodium concentrations more than 2–3 mEq/L below plasma sodium concentrations, the hypoosmolality is amplified by the effect of sodium loss through diffusion coupled with ultrafiltration. Neural and cardiovascular compensatory responses then become inadequate when ultrafiltration exceeds plasma refill ultimately leading to a fall in the blood pressure.

Dialysis against a higher dialysate sodium concentration promotes hemodynamic stability by improving ultrafiltration tolerance, both by increasing intravascular osmotic pressure and by improving vasoconstrictive compensatory responses [16]. But this hemodynamic benefit comes at the expense of volume expansion. When the dialysate sodium concentration exceeds the total plasma sodium concentration, the patient has excess of sodium content during treatment to increased weight gains and volume expansion.

Krautzig et al. lowered dialysate sodium from 140 to 135 mEq/l (over the course of 15–20 wk) and enforced a low salt diet in 8 HD patients, an intervention that resulted in a decrease in mean arterial pressure from 108 mmHg to 98 mmHg ( $P=0.02$ ) [17]. Farmer et al. decreased dialysate sodium by 5 mEq/L for 2 weeks in 10 HD patients and noted a fall in 24-h ambulatory BP from 141/83 mmHg to 133/78 mmHg ( $P=0.01$  for both systolic and diastolic BP) associated with a 33% decline in systemic vascular resistance [18]. In our study, there was significant reduction in occurrence of intradialytic Complication in Phase II when compared with Phase I. There was no Increase in hypotension or cramps in individualized sodium Phase (Phase II) despite the low sodium concentrations used during Dialysis. This was like the findings of Penne et al who in 55 patients they studied found significant difference with individualized sodium gradient and had no less Intradialytic complications [19].

The main concern with the method of individualized dialysate sodium prescription is the development of hyponatremia and hypo-

osmolality related complications because of the lack of sodium diffusion and the concomitant sodium losses by ultrafiltration. However, we observed the episodes of distressing symptoms (headache, cramps and hypotension) to be significantly decreased in the individualized sodium phase. Individualization of dialysate sodium mainly influences the IDWG and leads to better BP control in patients with poorly controlled BP. Hence, adjusting the dialysate sodium is a potential measure to reduce fluid overload in HD subjects and thus combat the dangers of LVH.

### CONCLUSION

Our study was aimed to investigate whether dialysis patients will have beneficial effects of individualized sodium profiling. It has been observed that individualized dialysate sodium was associated with significant reduction in interdialytic weight gain, ultrafiltration requirement, improvement in blood pressure and reduction in number of dialysis related complication in chronic HD patients. Long term studies are necessary to observe if these short-term benefits are sustained.

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