

## Review

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# Individualized Sodium Prescription in Hemodialysis: An Ally for Better Dialysis Outcomes?

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## ABSTRACT

The current practice in dialysis centres all over the world is to use standard sodium dialysate for all patients. Recently, there is a lot of interest in manipulating the dialysate sodium concentration to reduce fluid overload and achieve better cardiovascular outcomes. An ideal dialysate sodium concentration should provide intradialytic stability and abate the chronic volume and pressure overload that affects hemodialysis patients. Since the sodium set points in patients on hemodialysis is varied but individual specific, the focus is on individualized dialysate sodium prescription.

**KEYWORDS:** Hemodialysis, Sodium, Dialysis outcomes, Individualized dialysate.

**ABBREVIATIONS:** ECF: Extracellular fluid; IDWG: Interdialytic weight gain; LVH: Left Ventricular Hypertrophy; HD: Hemodialysis.

## INTRODUCTION

Sodium is the most abundant cation in extracellular fluid and hence, the major determinant of serum osmolality and Extracellular fluid (ECF) content. Hemodialysis patients are known to have a predialysis sodium level which is individual specific and different from sodium levels in a normal healthy individual.<sup>1</sup> Addition of extra sodium during hemodialysis influence Interdialytic weight gain (IDWG) and pre-dialysis blood pressure, which leads to higher volume and pressure overload, resulting in higher cardiovascular morbidity and mortality.<sup>2-12</sup>

## RELATIONSHIP BETWEEN SODIUM AND FLUID BALANCE IN HEMODIALYSIS PATIENTS

In advanced renal failure, urea and other nitrogenous waste accumulation causes increased plasma osmolality. But urea is readily diffusible between cell membranes and hence is an ineffective osmole, i.e. it cannot establish an osmolality gradient. Thus, even in uremic patients, sodium is the predominant determinant of serum osmolality and thus determines intracellular-intravascular fluid distribution, cell volumes, thirst and blood pressure.<sup>13</sup>

## THE CONCEPT OF SODIUM SET POINT IN DIALYSIS PATIENTS

It has been consistently observed that HD patients have a constant predialysis plasma sodium concentration, and they also seem to have an individualized osmolar set point.<sup>1,14</sup> This value is highly conserved. Addition of extra sodium to the body will increase the thirst, thus increasing fluid intake so as to maintain the sodium and osmolar setpoints. De Paula studied 27 patients on hemodialysis and found that their pre-HD sodium levels were same irrespective

of the dialysate sodium concentration which was used (standard Na<sup>+</sup> HD, 134.0±1.4 mEq/L; individualized Na<sup>+</sup> HD, 134.0±1.5 mEq/L; P= 0.735).<sup>2</sup> Table 1 shows the pre HD sodium values observed in various published studies.

#### SODIUM CONCENTRATION IN DIALYSATE

Dialysate is an artificial fluid which reconstitutes ECF by removal of urea and other waste products and transfer of electrolytes and water. In 1960's and 1970's, each dialysis session used to last 8-24 hours and contained low sodium levels of 126 mEq/L which removed 250-450 mEq salt ingested weekly.<sup>15</sup> With the advent of large surface area dialysers, dialysis became much more efficient and shorter. Use of hypotonic sodium solutions with the newer dialysers caused dialysis disequilibrium syndromes due to rapid reduction in plasma tonicity, characterised by nausea, vomiting, muscle cramps and hypotension. To combat this, between 1980 and 1995, dialysate sodium concentrations were progressively increased from 132 mEq/L to the current day 140-145 mEq/L.<sup>13</sup>

Use of high sodium dialysate (dialysate Na<sup>+</sup> concentration higher than plasma) is not without its share of problems. Flanigan showed that over a 1 year period, dialysis patients have a relatively sodium setpoint which varied from 132 to 144 mEq/L in different patients and when these patients are dialysed with 140 mEq/L sodium dialysate, their pre-dialysis to post-dialysis sodium increased by 2.3-3.6 mEq/L. Since the body attempts to maintain the sodium setpoint, even if water is removed during dialysis, these patients will drink more water during interdialytic period causing excess weight gain, increased ECF volumes and thus, higher blood pressures.<sup>13</sup>

#### IMPORTANCE OF FLUID OVERLOAD IN HEMODIALYSIS PATIENTS

The most common cause of death in dialysis patients is cardiovascular cause, mostly due to lethal arrhythmia and the key condition associated with this is Left Ventricular Hypertrophy (LVH).<sup>16-18</sup> Left Ventricular Hypertrophy leads to activation of myocardial fibrosis pathways, which in turn leads to stiffened myocardium prone to dilated cardiomyopathy and aberrant conduction. Some studies have shown that regression in left ventricular mass occur with improvements in BP control and extracellular fluid volume.<sup>19,20</sup> As discussed earlier, sodium is the major determinant of extracellular volume. In dialysis patients, sodium is added to the body either *via* dietary intake or from dialysate. Hence, adjusting the dialysate sodium is an attractive measure to combat the dangers of LVH.

#### ALTERING THE HEMODIALYSIS SODIUM PRESCRIPTION FOR REDUCING SODIUM LOAD

An ideal dialysate sodium concentration should maintain sodium setpoint, optimize intradialytic stability and abate the chronic volume and pressure overload that affects hemodi-

alysis patients. Too much of sodium in dialysate fluid can lead to complications as described above and too less can lead to intradialytic hypotension.<sup>21,22</sup> In hemodialysis patients, dialysate sodium minus pre-dialysis plasma sodium concentration ( $\delta$ DPNa<sup>+</sup>) and post-dialysis minus pre-dialysis plasma sodium ( $\delta$ PNa<sup>+</sup>) are taken as surrogates of sodium balance.

Sodium modeling programs are available on dialysis machines and allow alteration of sodium concentration over time. In eunatraemic dialysis, the diffusive sodium concentration gradient is neutralized to eliminate diffusive sodium fluxes. The diffusible sodium concentration is decided by several factors like plasma water sodium activity, charge characteristics, quantity of plasma proteins (Gibbs-Donnan effect), pH gradient across the dialyser membrane and sodium reflection coefficient of the dialysis membrane.<sup>23</sup> This will typically result in a 'eunatraemic' dialysate Na<sup>+</sup> concentration of 1.5-5 mEq below the plasma concentration recorded by flame photometry or indirect potentiometry, which will cause no sodium loss or gain to blood.<sup>23</sup> Gibbs-Donnan effect in hemodialysis occurs due to nondiffusible, negatively charged plasma proteins which create an electric field that attracts sodium, thus reducing the diffusion of sodium from plasma across the dialysis membrane.<sup>24</sup> Hence, a correction factor of 0.95 (Donnan Coefficient) is applied to plasma sodium to get the dialysate sodium value which will result in eunatraemic dialysis.<sup>23</sup>

#### CLINICAL EXPERIENCE WITH INDIVIDUALIZED SODIUM DIALYSATE

Several studies have shown that dialysate sodium prescriptions individualized to each patient's sodium set point can be beneficial (Table 1). De Paula et al. prospectively studied 27 hemodialysis patients in a single-blind crossover study. Subjects underwent nine consecutive HD sessions with the dialysate Na<sup>+</sup> concentration set to 138 mEq/L (standard Na<sup>+</sup> HD), followed by nine sessions wherein the dialysate Na<sup>+</sup> was set to match the patients average pre-HD plasma Na<sup>+</sup> measured three times during the standard Na<sup>+</sup> phase multiplied by 0.95 (individualized dialysate Na<sup>+</sup> HD). There was decrease in Interdialytic weight gain (IDWG), interdialytic thirst scores, and episodes of intradialytic hypotension in individualized Na<sup>+</sup> phase compared with the standard phase.<sup>25</sup>

The results from other studies have been mostly similar. In an observational study with a facility level decrease in dialysate [Na<sup>+</sup>] from 141 mmol/l to 138 mmol/l, Thein et al. found no difference in IDWG but decrease in pre and post-dialysis systolic and diastolic BP, pre-dialysis plasma [Na<sup>+</sup>].<sup>26</sup> Aramreddy et al. reported on a case series of 13 patients undergoing thrice-weekly in-center hemodialysis with an individualized dialysate Na<sup>+</sup> prescription in whom dialysate Na<sup>+</sup> concentration was 2 mEq/L lower than average plasma Na<sup>+</sup> over the preceding 3 months. Individualized dialysate Na<sup>+</sup> was achieved in all patients through a stepwise weekly reduction of the standard dialysate Na<sup>+</sup> prescription (140 mEq/L) by 2-3 mEq/L until reaching a

Na<sup>+</sup> gradient of -2 mEq/L (dialysate Na<sup>+</sup> minus average plasma Na<sup>+</sup> over the preceding 3 months). They found that individualized reduction of dialysate Na<sup>+</sup> reduces IDWG without significantly increasing frequency of cramps or hypotension.<sup>27</sup> Similar results have been obtained by Elshahawy et al. who studied 40 stable chronic HD patients in a single-blind crossover design. Individualized dialysate Na<sup>+</sup> concentration was associated with a decrease in IDWG and dialysis hypotension and related symptoms and better BP control in stable chronic HD patients.<sup>28</sup>

Individualizing sodium is found to be of benefit only in patients with sodium set point below the standard sodium in dialysate (usually 138-140 mEq/L). Kim et al. studied 19 patients on hemodialysis who were dialysed with individualized sodium concentration matching their serum sodium level. 13 of these patients had serum sodium higher than standard dialysate sodium. On implementation of sodium alignment, their thirst scores and interdialytic weight gain increased, with no effect on blood pressures or intradialytic complications.<sup>29</sup> Table 1 summarises the results from these studies on sodium modelling.

**CONCLUSION**

Dialysate sodium as a contributor to hypertension in patients on Hemodialysis (HD) has been unforeseen many a times. Recent data suggest that tailoring the dialysate sodium to individual's sodium setpoint has the potential for short and long term benefits for patients. Large scale randomized controlled trials are urgently required to convincingly prove the safety and efficacy of this very practical and easily implementable change in dialysis practice.

**CONFLICTS OF INTEREST:** None.

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Study group	Reference no.	Mean Pre HD Na <sup>+</sup> level (mEq/L)	Intervention	Result
de Paula et al.	2	134	Compared standard dialysate phase (138 mEq/L) with individualized sodium phase (patients average pre-HD plasma Na <sup>+</sup> measured three times during the standard Na <sup>+</sup> phase multiplied by 0.95 )	Decrease in interdialytic weight gain, interdialytic thirst scores, and episodes of intradialytic hypotension in the individualized Na <sup>+</sup> period. Pre-HD BP was lower in individualized Na <sup>+</sup> HD in patients with uncontrolled BP at baseline.
Thein et al.	26	139.7	Facility level decrease in dialysate [Na <sup>+</sup> ] from 141 mmol/l to 138 mmol/l	Change in dialysate [Na <sup>+</sup> ] was associated with a statistically significant small to medium-sized decrease in pre- and post-dialysis systolic and diastolic BP, pre-dialysis plasma [Na <sup>+</sup> ], but not IDWG. Change was greatest in the patient tertile with the highest initial BP.
Aramreddy et al.	27	135.3	Individualized dialysate Na <sup>+</sup> achieved in patients through a stepwise weekly reduction of the standard dialysate Na <sup>+</sup> prescription (140 mEq/L) by 2-3 mEq/L until reaching a Na <sup>+</sup> gradient of -2 mEq/L (dialysate Na <sup>+</sup> minus average plasma Na <sup>+</sup> over the preceding 3 months).	Decrease in IDWG% with no change in pre- or post-HD systolic or diastolic blood pressures, cramps, intradialytic hypotension.
Elshahawy Y et al.	28	137.45	Standard Na <sup>+</sup> (138mEq/L versus individualized Na <sup>+</sup> (midweek pre-HD measured Na <sup>+</sup> by the Donnan coefficient of 0.95)	Lower IDWG, intradialytic hypotension, cramps and related, post-HD Na <sup>+</sup> and better blood pressure control in individualized sodium group.
Jung ES et al.	29	140.1 in 'high sodium' group and 136.7 in 'equal sodium' group	Standard period (dialysis sodium concentrations were set at 136 (n= 15) or 138 mmol/L (n=4) versus individualized period (dialysate sodium levels aligned to individual serum sodium levels)	Increasing the dialysate sodium concentration based on serum sodium concentrations exacerbated weight gain and thirst in patients with negative sodium gradients.

**Table 1:** Clinical results of sodium modelling during hemodialysis.

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