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| **STUDY PROTOCOL** |

**STUDY TITLE:**  The effect of low dialysate sodium on interdialytic weight gain (IDWG) and hypertension in patients undergoing chronic intermittent haemodialysis – a prospective study in The Townsville Hospital and the North Ward haemodialysis units.

**SHORT TITLE OR ACRONYM:** The effect of lowering dialysate sodium concentration on hypertension and weight gain in patients on maintenance haemodialysis.

**LAY DESCRIPTION OF THE PROJECT:** This prospective study aims to observe the effects of lowering the sodium concentration in the dialysate fluid by 4mEq/L, on hypertension and IDWG in patients undergoing chronic intermittent haemodialysis for end stage renal disease (ESRD) in The Townsville Hospital and the North Ward haemodialysis unit.

**WORDING TO STATE STUDY WILL BE CONDUCTED IN COMPLIANCE RELEVANT LEGISLATION AND GUIDANCE DOCUMENTS**

As a principal investigator I will ensure that his retrospective study is compliant with:

* Professional Code of Conduct
* All the requirements as defined by AHPRA
* Current best practices in the field of nephrology
* Current best practice in ethics
* State and commonwealth acts and legislations
* Our hospital policies and procedures

**STUDY INVESTIGATOR(S)**

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1. **INTRODUCTION**

Inadequate sodium removal in intermittent haemodialysis is responsible for IDWG and hypertension. This aggravates hypertension, worsening the adverse cardiovascular mortality associated with ESRD. (1) The intermittent, thrice weekly haemodialysis is associated with reduced survival when compared to patients on short daily dialysis and home dialysis. This major drawback of intermittent haemodialysis was first pointed by Kjellstrand et al. in 1975. (2) There are several studies supporting the evidence that longer dialysis sessions improve survival, including observational data over a period of 25 years. (2,3)

Current dialysis prescriptions use sodium concentrations that are somewhat higher than the patient’s plasma concentration leading to the net influx of sodium from dialysate. This leads to a higher sodium concentration of sodium after haemodialysis – the key factor in increased thirst and subsequent intravascular volume expansion. (6)  The IDWG can be improved by reducing salt intake and the studies suggest that this is one of the most important interventions to achieve normovolemia and hypertension control in patients undergoing intermittent haemodialysis. Reducing salt intake can be difficult to achieve in patients with ESRD hence unconventional approach is warranted to tackle the problem of sodium overload. Sodium removal in haemodialysis can be achieved by higher ultrafiltration volumes or by reducing dialysate sodium concentration. The lower dialysate sodium seems to be a simple method of reducing IDWG and hypertension, and this alternative needs further study and consideration. (9,10)

1. **BACKGROUND**

Body sodium is compartmentalised into two fractions – the osmotically active intravascular fraction and the osmotically inactive intracellular (extravascular) fraction – the former leads to expansion of the intravascular compartment and the latter results in chronic vascular smooth muscle contraction; hence both contribute to increase in blood pressure by different mechanisms. (1-3)  Charra B et al. demonstrated an interesting relationship between intravascular volume and the blood pressure response during the first year of haemodialysis. In a study including 712 patients an initial decline in the intravascular volume resulted in an initial reduction of 2 to 3 kilogram weight and was associated with a rapid blood pressure drop. As the dialysis continued further and the dry weight was achieved, no further weight loss occurred; however, there was a second dip in blood pressure at 2 months duration. This second dip blood pressure is best explained by vascular remodelling due to decrease in intracellular sodium concentration resulting in a decrease in peripheral resistance; a process which can takes up to eight weeks. (1,4,5)

As mentioned earlier current dialysis prescriptions use sodium concentrations above physiological range leading to the net sodium gain during dialysis. This leads to increased thirst and subsequent intravascular volume expansion. (6)  Due to the of lack of availability of effective dialysers, and the delivery systems which were incapable of achieving ultrafiltration the traditional dialysis prescriptions used lower sodium concentrations. This allowed effective sodium removal during dialysis and achieved excellent control of blood pressure, IDWG, and suppression of thirst. The dialysis sessions were long and majority of patients on maintenance haemodialysis were normotensive. We have seen this in the literature reported from Tassin where exceptional blood pressure control and better survival were achieved in patients on maintenance haemodialysis. Their dialysis centres still use low dialysate sodium (138mEq/L) combined with salt restriction of less than 5 gram a day. (7)

After the dialyser quality improved and effective delivery systems were introduced in 1970s the dialysis disequilibrium syndrome was reported increasingly by physicians. Because of more effective haemodialysis the low dialysate sodium was not essential anymore and there was a slow inclination towards prescribing physiological range dialysate sodium. Gradually over decades the dialysate prescriptions used higher sodium to avoid dialysis disequilibrium and other adverse effects. The use of high dialysate sodium significantly reduced the incidence of dialysis disequilibrium syndrome, and other unwanted adverse effects including nausea, vomiting, cramps, headache, hypotension, and chest pain.(8)  The IDWG can be improved by reducing salt intake which can be difficult to achieve in patients with ESRD especially in patients with non-compliance. Hence unconventional approach (lowering dialysate sodium) is warranted to tackle the problem of sodium overload. The option of lower dialysate sodium needs further exploration. (9, 10)

Regular hemodialysis is a very physically, and mentally, demanding therapy. As part of the treatment, patients need to stick to very strict fluid and dietary restriction on top of their many regular medications. As such, patient compliance is frequently an issue. Poor adherence makes hypertension and IDWG difficult to control. This warrants unconventional methods like lowering the dialysate sodium for reducing thirst and achieving IDWG and hypertension control.

During the last decade there has been an increasing interest in researchers on dialysate sodium to study its effect on hypertension and IDWG. Most of these studies have shown a favourable effect on hypertension and a few have demonstrated improvement in IDWG. (9-18)

Santo et al. did an in-depth review of the literature available on low dialysate sodium, and its impact on hypertension and IDWG. (9) Krautzig S et al. demonstrated a drop of 10 mmHg in the mean arterial blood pressure after 5 mEq/L reduction in dialysate sodium over a period of 15 to 20 weeks. (13) Similar improvements in blood pressure were noted in the other studies after the dialysate sodium was dropped by 5 mEq/L. (11,12) While most studies showed improvement in blood pressure, the study by Kooman et al. demonstrate no change in blood pressure. (10) Some studies clearly demonstrated significant improvement IDWG in addiction to blood pressure control. (14-17)

Sayarlioglu et al. lowered the dialysate sodium based on the patient’s serum sodium levels. The patients with a sodium concentration lower than 137mEq/L were prescribed dialysate sodium of 135 mEq/L and those with the sodium level of more than 137mEq/L were prescribed dialysate sodium of 137 mEq/L. After 8 weeks there was a significant decrease in blood pressure. (16)

Davenport performed an audit in 7 centres which included 469 patients and used different dialysate sodium concentrations ranging from 136.8 mEq/L to 140mEq/L and demonstrated that lower dialysate sodium was associated with lower pre and post-dialytic weight gain, and required lesser antihypertensive agents. Interdialytic hypotensive events were not different among the two groups. (19)

Thein H et al. retrospectively analysed the data from a single dialysis centre before and after the default dialysate sodium was dropped from 141 mEq/L to 138 mEq/L. The study demonstrated a modest drop in blood pressure of 5 mmHg, and greater in patients with higher blood pressures.

After the intervention, however there were no changes in IDWG. The intervention was well tolerated and no increase in hypotensive episodes occurred even in patients with pre-existing hypotension (20)

In addition to its effects on interdialytic weight gain and improved sodium clearance, low dialysate sodium may also have additional beneficial effects. Kutlugun A et al. demonstrated in their study that in addition to reduction in interdialytic weight gain and better hypertension control, lower dialysate sodium also improved endothelial dysfunction. (21)

Beneficial effects of lower dialysate sodium have also been demonstrated in Peritoneal Dialysis also. Low sodium solutions were directly compared with standard sodium solutions, and the former achieved better sodium removal and improved intravascular volume status of patients. (22,23)

While there are many studies in favour of lower dialysate sodium and demonstrate its role in improving sodium profile and IDWG, an observational study by Hecking M et al. showed confrontational results. While there was a modest improvement in IDWG, the study demonstrated a lower risk of death and lower hospitalization rates with high dialysate sodium. (24)

1. **AIM(S) OF STUDY**
   1. **Primary Aim:** To observe the effects of lowering the dialysate sodium on IDWG and hypertension in patients undergoing chronic intermittent haemodialysis for ESRD.
   2. **Secondary Aims:** To observe the changes in the antihypertensive medication and the number of hypotensive episodes, if any, after the intervention.
2. **OBJECTIVE(S)** 
   1. **Primary Objective:** To study the safety and authenticity of lower dialysate sodium as an alternative to improve IDWG and hypertension control in patients undergoing chronic intermittent haemodialysis for ESRD.
3. **HYPOTHESI(E)S** 
   1. **Primary Hypotheses:** Lower dialysate sodium is a simple and useful alternative to salt and water restriction as a measure to control IDWG and hypertension in ESRD patients. Lowering the dialysate sodium by 5mEq/L has been shown to reduce blood pressure by 5 to 10 mmHg. It also reduces thirst and improves blood pressure control.
   2. **Secondary Hypotheses:** Lower dialysate sodium leads to improvement in blood pressure control and likely higher incidence of hypotensive episodes in patients prone for hypotension. There is some weak evidence for this; however, it needs further validation.
4. **STUDY DESIGN**

This prospective study will evaluate the effect of reducing dialysate sodium on IDWG and hypertension in a subgroup of regular haemodialysis patients.

1. **STUDY SETTING/LOCATION(S)**

This single-centre study will be conducted within The Townsville Hospital haemodialysis units – this includes the satellite haemodialysis unit at the North Ward Site.

1. **STUDY DURATION**

The total duration of the study will be two years in length. Patient recruitment, intervention, and data collection will make up the first 8 weeks of this timeframe. This timeline was chosen based on the data and results from previous studies. The response to hypertension after reducing dialysate sodium occurs in two phases – the first which is immediate, and happens as the intravascular volume reduces. This is due to reduced salt burden. The second phase is seen 6 to 8 weeks later, and is due to vascular remodelling in the setting of reduced salt concentration in the extravascular compartment. The remainder of the proposed study time will be used for data analysis, and preparation for presentation/journal submission.

1. **STUDY POPULATION** 
   1. **Recruitment Process:** Patients on maintenance haemodialysis for ESRD deemed eligible based on the below inclusion/exclusion criteria, will be approached by the research team. Due to the patient demographics of the THHS dialysis units, the majority of our study participants will be Aboriginal and Torres Strait Islander (ATSI). The Aboriginal and Torres Strait Islander Health Liaison Service (ATSIHLS) at THHS have agreed to be directly involved in consenting of all study participants. To maintain consistency, the ATSIHLS staff will be involved in process for all patients - those that are ATSI, and those that are not. As such, consent will be done by medical staff (nurses/medical doctor) in conjunction with the ATSIHLS staff. The ATSIHLS staff will help mitigate potential coercion based on existing patient-medical staff relationships, and promote cultural sensitivity where necessary. Copies of the informed consent documents will be given to the patient, stored as hardcopies, and uploaded into the patient's electronic medical record (EMR).
   2. **Inclusion criteria:**

1. Patients aged above 18 years

2. Patients on maintenance haemodialysis for at least 6 months

3. Patients with significant IDWG (2 kilogram or more) with or without associated uncontrolled hypertension

4. Patients who are medically stable with no other acute issues that can affect the study outcome

* 1. **Exclusion criteria:**

1. Patients who have cardiac failure and cardiovascular compromise

2. Patients who have other acute issues (e.g. sepsis, hypotension of any cause, hyponatremia with serum sodium less than 135 etc.)

3. Patients prone for hypotension

4. Patients who are pregnant

5. Patients who are homeless

* 1. **Potential for Risk, burdens and benefits:**

*Benefits:* This study will improve insight into the role of low dialysate sodium in reducing the IDWG and hypertension in patients on haemodialysis. Therapy compliance in dialysis patients is poor. As such higher IDWG and unsatisfactory blood pressure control is very common. There is need for unconventional methods like lower dialysate sodium which has shown to improve blood pressure control and IDWG, and needs further studies and validation.

*Risks:* There is a small risk of adverse effects like nausea, vomiting, cramps, headache, hypotension, and chest pain. Dialysis disequilibrium syndrome (DDS) is an extremely rare complication and can manifest as a seizure in its worse form. This adverse effect is highly unlikely in patients undergoing chronic intermittent dialysis. The dialysate sodium will be gradually decreased at the rate of 2mEq/L per week to a total of 4mEq/L at the end of second week – this makes the serious complications highly unlikely. Some of the studies done in recent times have not reported DDS even with a drop of sodium by 5mEq/L. Also, many dialysis centres use sodium of 137 routinely as a part of the hospital protocol and DDS is not reported from these centres with routine dialysis use.

1. **STUDY OUTCOMES** 
   1. **Primary Outcome:** Improvement in IDWG and hypertension after reduction in dialysate sodium (by 4mEq/L).
   2. **Secondary Outcomes:** Incidence of hypotensive events (interdialytic and postdialytic) and other adverse effects including, nausea, cramps, headache and DDS.
2. **STUDY PROCEDURES** 
   1. **Recruitment and consent of participants:** Patients deemed eligible as per the inclusion/exclusion criteria will be identified by the principal, and co-investigators only. Patients will not be approached by any staff until their eligibility has been assessed by one of the study investigators. As such, staff that are unfamiliar with the study will not be involved in the recruitment of patients unless instructed by the principal/co-investigators. As mentioned in section “9.1 - Recruitment Process”, the consenting process will involve medical staff and the Aboriginal and Torres Strait Islander Health Liaison Service staff. Please refer to section 9.1 for a more in-depth explanation of the recruitment and consenting of study participants.
   2. **Withdrawal of participants from a study:** Patients experiencing significant side effects or serious complication will be withdrawn from the study. Participation in this study is completely voluntary and patients can withdraw from the study at any time during the study. Patients who wish to discontinue for any other reason will be withdrawn from the study.
   3. **Measurement tools used:** Changes in blood pressure and IDWG before and after intervention. The average IDWG of the patients will be recorded 8 weeks before the intervention and will be compared with the average IDWG post intervention.
   4. **Data management:** All study data will be uploaded, and stored in EMR. During the data acquisition phase of the study, this will allow any medical/allied health staff involved in the study participant’s care to be aware of the patient's enrollment in the study. This will also allow our safety monitor access to the study participant’s data during the course of the intervention to assess for any adverse effects/outcomes. Once the data acquisition period is over, the data will be extracted, de-identified, and stored in a password-protected Microsoft Excel document. This document will only be available to the study investigators. The data will be kept for a period of 7-years following conclusion of the study, at which point it will be deleted/destroyed.
   5. **Safety considerations/Patient safety:** Patients will be closely monitored for all hypotensive events (interdialytic and postdialytic), as well as any other adverse events including: nausea, cramps, headache and dialysis disequilibrium syndrome – a very rare condition. The dialysate sodium will be reduced 2mEq/L per week (4mEq/L in total) which makes this complication very unlikely. Many studies done recently have not reported DDS even with a 5mEq/L drop of sodium.
   6. **Data monitoring:** During the recruitment, and data acquisition phase, all data will be monitored and documented in EMR. Once in the data analysis phase, data will be deidentified, and stored in a password-protected Microsoft Excel document. Please refer to section 11.4 - Data Management for further details.
   7. **Stopping rule:** Any patient that experiences significant side-effect related to dialysate sodium (as listed above) will be withdrawn from the study. Likewise, if the patient wishes to withdraw at any stage, for any reason, they may do so. Data of withdrawn patients will be kept by the study authors.
3. **SAMPLE SIZE AND DATA ANALYSIS**
   1. **Sample size and statistical power**: The study population will be patients with significant IDWG at the dialysis unit in the Townsville Hospital and at the North Ward satellite unit. If the true difference in the experimental and control means is 0.6, the study will need 44 subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05 (Sample size calculated using openepi version 3. The mean weight gain and SD for sample size calculations were based on the study by *Mendoza JM, et al. Effect of Lowering Dialysate Sodium Concentration on Interdialytic Weight Gain and Blood Pressure in Patients undergoing Thrice-weekly In-Centre Nocturnal Hemodialysis: A Quality Improvement Study).* Clinical experience suggets the total number of patient meeting the inclusion criteria will be small (25 to 40 approximately). That being said, if the results are significant it can improve insight into the lower dialysate sodium and IDWG relationship. This will be of great benefit to any patients where treatment non-compliance is an issue.

**Data analysis plan**:

Data will be collected from electronic medical records. Data collected will include – patient demographics, pre- and post-dialytic weight and blood pressure, changes in blood pressure, and any other adverse events (as previously mentioned). The principal investigator will be primarily responsible for collecting the data, monitoring patients for adverse events, and using SPSS software to analyse collected data. Continuous variables will be tested for normality. Based on the outcome of the test parametric students T test or non-parametric Mann-Whitney test will be carried out to determine the significant differences in weight gain. Paired tests will be carried out to determine differences in weight gain among the patients during and after the treatment. Categorical data will be analysed using the Chi-squared analysis. Bivariate analysis would be performed for determining the confounding factors. Where appropriate multivariate tests will be carried out, a p value < 0.05 will be considered statistically significant.

1. **ETHICAL CONSIDERATIONS**

Although no specific population is being targeted, a large portion of study participants will be Aboriginal and Torres Strait Islander. This is simply because of the patient demographics of the renal unit at The Townsville Hospital. The Aboriginal and Torres Strait Islander Health Service at The Townsville Hospital are involved in our study, and have agreed to support this project. The service will have an active role in overseeing the study, as well as in the recruitment of study participants.

1. **DISSEMINATION OF RESULTS AND PUBLICATIONS**

The results of this study may be presented at national/international scientific conferences and/or published in a medical journal.

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