PREVALENCE OF HYPONATREMIA IN PATIENTS ADMITTED WITH HEART FAILURE AT THE KENYATTA NATIONAL HOSPITAL

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DECLARATION

I declare that this dissertation is my original work and to the best of my knowledge has not been presented for the award of a degree at any other university.

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LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitors
ACTH	Adrenocorticotropic Hormone
ARB	Angiotensin Receptor Blockers
AVP	Arginine Vasopressin
GFR	Glomerular Filtration Rate
KNH	Kenyatta National Hospital
HF	Heart Failure
NKCC	Natrium (sodium) Kalium (potassium) Chloride Channels
NYHA	New York Heart Association
RAAS	Renin Angiotensin Aldosterone System
SON	Supra Optic Neuron
SNS	Sympathetic Nervous System

ABSTRACT

Background

Hyponatremia is a common electrolyte disturbance in hospitalized patients with heart failure. It is associated with high morbidity, longer in-hospital stay and is a well known predictor of mortality in patients with heart failure. There is a paucity of data on the prevalence of hyponatremia in patients with heart failure in Kenya.

Objectives

The aim of the study was to determine the prevalence of hyponatremia in patients admitted with heart failure in the medical wards at the Kenyatta National Hospital.

Methodology

This was a prospective, observational cohort study conducted over a period of about 3 months in patients above 13 years with heart failure in the medical wards. Patients were screened using the Modified Framingham 'Criteria for eligibility and recruited upon signing an informed consent or assent. Sodium levels were done within 24 hours of admission and patients were followed up to determine their outcome at two weeks. The outcomes included, in hospital mortality, discharged home and prolonged stay in hospital beyond the 2 weeks.

Results

The study was conducted from December 2015 to February 2016. Eighty nine patients with heart failure based on the Modified Framingham's Criteria were recruited. 53.9% were males and the mean age of the patients was 51.6±18.8 years with a range of 14-86 years. On admission 94.4% of the patients were in NYHA class 3 and 4. 79.8% (95% CI 71.9-87.6) of the patients had hyponatremia at admission. The mean sodium level was 128.2±8.1 mmol/L. Of these, 84.3% were on a loop diuretic at admission while 6.7% were on a thiazide diuretic. During the 2 week follow up period, 13.5% of all the patients admitted with heart failure died while 48.5% were discharged from the hospital. 38.2% of the patients had a prolonged stay and were still undergoing treatment at the lapse of the 2 weeks. Of those who died 66.7% had hyponatremia while 88.2% of those who were still admitted at the lapse of the 2 weeks had hyponatremia.

Conclusion

This study found a high prevalence of hyponatremia in patients admitted with heart failure at the KNH. Hyponatremia did not affect the short term outcomes in a statistically significant way; however, the trend suggests worse outcomes in the hyponatremia patients.

CHAPTER 1

1.0 INTRODUCTION

Heart failure is a clinical syndrome that occurs in patients who, because of an inherited or acquired abnormality, the heart cannot maintain an adequate cardiac output to maintain the patients metabolic demands or can do so only at the expense of an elevated filling pressure (1).

Heart failure is a major public health problem worldwide (2). The burden of heart failure varies considerably between regions of the world. Heart failure affects about 2% of the western population with prevalence increasing sharply from 1% in 40 year olds to 10% above 75 years. It is the most common cause of hospitalization in patients over 65 years of age (3). In the USA, the prevalence of heart failure is expected to rise by 25% by the year 2030 (4). In sub-Saharan Africa heart failure has been recognized as a significant contributor to cardiovascular disease burden for many decades. There are no population based studies in sub Saharan Africa. In a hospital based study in Port Harcourt in Nigeria, heart failure constituted 9.6 % of all medical admissions (5). In another study done in KNH showed that congestive heart failure constitutes about 3.3% of all medical admissions and the commonest cause of heart failure was rheumatic heart disease (5). Urbanization, changes in lifestyle and an increasingly aging population, the spectrum of causes of heart failure has expanded resulting in a significant burden in both the non communicable and communicable etiologies (6).

Electrolyte disturbances are frequent and potentially hazardous complications of heart failure. Heart failure provides a perfect milieu for the development of these disturbances. Renal dysfunction, elevation of neurohormonal substances, activation of the rennin-angiotensin-aldosterone axis ,complications of therapy with diuretics, cardiac glycosides or ACE inhibitor are all contributing factors (7).

Hyponatremia is the most common electrolyte abnormality encountered in clinical practice both in- hospital and ambulatory setting (8). Hyponatremia has a prevalence of about 1.72 % in the general population (9).It has a prevalence of 4% to 45% in acute hospital setting (5). Hyponatremia has a wide spectrum of clinical symptoms from subtle to severe, a potential for significant mortality, morbidity and increased length of hospital stay in patients presenting with a

range of conditions (10). The most important complication is the development of cerebral oedema, with headaches, nausea, vomiting, seizures and coma (11). In acute symptomatic hyponatremia, serum sodium concentrations decrease rapidly resulting in the appearance of neurological symptoms. Mortality rates associated with hyponatremia range from 5-50 % depending on the severity and acuity of onset (12). Hyponatremia is, therefore, both common and important.

Hyponatremia in patients with heart failure has been related to adverse outcome and it is considered to be an independent predictor of poor prognosis (13–15). Hyponatremia in heart failure is associated with increased short term and long term morbidity as well as significantly higher rates of in-hospital mortality, increased rate of re-hospitalization (16), increased hospital resource use and longer hospital stay (10,13).

Even mild hyponatremia among patients with heart failure regardless of ventricular function is associated with high in-hospital and post discharge mortality, prolonged hospital length of stay and frequent re-hospitalization (17).

Electrolyte abnormalities are frequently overlooked in heart failure patients. Most of the available data on hyponatremia in heart failure are from America, Asia and Europe, which is genetically and environmentally different from our population. The cardiac morbidity could also be different in our environment. It would therefore be imperative to see if patients in our population behave similarly to neurohormonal changes and if hyponatremia is an equally important prognostic marker of short term adverse outcome in heart failure.

CHAPTER 2

2.0 LITERATURE REVIEW

Hyponatremia defined as a serum sodium ion concentration below 135 mmol/L (18) is a common phenomenon in patients with heart failure especially those admitted with decompensated heart failure (19). Hyponatremia is considered “mild” when the serum sodium concentration is between 130 and 134mmol/L, “moderate” as a concentration between 125 and 129 mmol/L and “profound ”as a concentration less than 125 mmol/L (18). Serum sodium concentrations and osmolality are maintained under precise control by homeostatic mechanisms that include stimulation of thirst, secretion of vasopressin and renal handling of filtered sodium (20).

Hyponatremia can be associated with low, normal or high tonicity as opposed to hypernatremia that always denotes hypertonicity. Tonicity refers to the contribution to osmolality of solutes such as sodium and glucose that do not move freely across cell membranes. Changes in serum osmolality are responsible for the signs and symptoms of hyponatremia and also for the complications that happen during treatment in the presence of high risk factors (19).

In general, hyponatremia results from a relative excess of water compared to sodium and according to the underlying mechanism, it is classified into dilutional or depletional (19). Dilutional hyponatremia is by far the most common form of the disorder, is usually caused by water retention. Depletional hyponatremia, in contrast, is caused by a decrease in sodium reserves, because of gastrointestinal, renal, cutaneous or blood losses.

2.1 Physiology of Water Handling

Understanding the normal, basic physiology of renal salt and water handling is vital in order to appreciate the pathophysiology of hyponatremia in heart failure.

Essentially all cases of true hyponatremia represent a failure to excrete maximally dilute urine except in the case of psychogenic polydipsia and low dietary solute. In the presence of normal renal function, this failure is most often related to the action of arginine vasopressin (AVP).

AVP is a peptide hormone synthesized in the supraoptic neuron (SON) and paraventricular nuclei of the hypothalamus. Subsequently, it is transported down axon terminals through the supraoptic hypophyseal tract where it is stored and released from the posterior pituitary (21).

Its effects are numerous and coupled to the effector receptor. When AVP binds to V1a receptor, it leads to vascular smooth muscle contraction while its effect on V2 receptors in the renal medulla leads to free water reabsorption by the collecting duct (22).

When AVP binds to V2 receptors, which are located on the basolateral membrane of the cortical collecting ducts leads to increased aquaporin 2 (aqp-2) mRNA levels and translocation of aqp-2 to the apical membranes (21). This increases tubular water permeability and allows water to move from the tubule to the medullary interstitium, resulting in a net reabsorption of free water. This movement of water is passive and relies upon a hypertonic renal medulla, generation of which is dependent on the activity of NKCC channels in the ascending loop of Henle (19). The absence of AVP as occurs in diabetes insipidus leads to loss of high volume of dilute urine.

AVP release is mediated by both osmotic as well as cardiac output and intravascular volume stimuli. The most potent stimulus for vasopressin release is an increased plasma osmolality (23). There are osmoreceptors in the supra optic nuclei that are exceedingly sensitive to changes in serum osmolality demonstrating alterations in AVP release in response to a 1% fluctuation in serum osmolality (21). This sensitivity serves to keep serum osmolality tightly controlled within a threshold for release of AVP of approximately 280 mOsm/Kg (24). This helps keep osmolality finely controlled in the range of 275-290 mOsm/Kg (23).

The nonosmotic stimuli for AVP release consists of the decline in cardiac output, intravascular blood volume or blood pressure (24). These stimuli, mediated through high and low pressure baroreceptor enhance the secretion of AVP for any given osmotic stimulus. In effect AVP will be released at a lower plasma osmolality when decreased intravascular volume, cardiac output or blood pressures are detected. Endogenous agents including acetylcholine, angiotensin II, histamine, bradykinin, neuropeptide Y have all been implicated in stimulation of AVP.

2.2 Pathophysiology

In the normal physiology, variations in serum osmolality is mainly regulated by AVP, renal responsiveness to AVP and thirst (24). The variation in serum osmolality serves as the main control of arginine vasopressin release. However in some conditions, as is the case in heart failure there is no osmotic stimulation of AVP release. In this case, a decrease in cardiac output leads to the continued release of AVP despite reduction in osmolality. In heart failure, patients' exhibit increased AVP production and generally a dysregulation of AVP characterized by an elevation of its level despite the presence of volume overload, atrial distension and low plasma osmolality (25). This causes retention of both sodium and water causing hyponatremia.

There are many mechanisms that are implicated in the pathogenesis of hyponatremia in heart failure. These include activation of the neurohormonal mechanisms, non osmotic release of arginine-vasopressin as well as by the heart failure medicine.

Heart failure leads to a decrease in cardiac output. This leads to arterial underfilling that in turn results in a decrease in the baroreceptor stretch located in the carotid sinus, renal afferent arteriole and aortic arch (26,27). This, in turn, leads to activation of the sympathetic nervous system and of the RAAS that result in peripheral and renal vasoconstriction. RAAS stimulation through the effects of angiotensin II causes an increase in resistance of afferent arterioles causing a decline in glomerular filtration rate, thus increasing sodium and water reabsorption in the proximal convoluted tubule. Angiotensin II induces aldosterone release from the adrenal gland further causing sodium retention (26,28). Angiotensin II also stimulates the thirst centre of the brain increases water intake and also stimulates the release of AVP. AVP binds to vasopressin-2 (V2) receptor subtype and increases the number of aquaporin-2 water channels leading to increased permeability of water in the collecting duct and enhanced free water retention (24,29).

Reduction in GFR is frequent among patients with heart failure and can lead eventually to a reduced capacity for water and Na+ excretion. The filtered load of Na+ decreases in parallel with declining GFR in patients receiving diuretics (30). Salt intake in these patients exacerbates volume overload and heart failure; they are also at risk of worsening hyponatremia with increased free water intake (31).

2.2.1 Role of Diuretics

The use of diuretics is the mainstay of treatment in patients with heart failure with fluid overload. Loop diuretics are preferred because they increase electrolyte free water clearance (32).

Diuretics are one of the most common causes of severe hyponatremia (33,34). Diuretics are prescribed in about 85-100% of symptomatic and in 16-35% of asymptomatic patients with heart failure (35). It is clear that most cases are caused by thiazide diuretics rather than loop diuretics and that severe hyponatremia can develop very rapidly in susceptible patient (36). In the general population, diuretic-induced hyponatremia is very common with thiazide accounting for the 63% of the cases of hyponatremia, loop diuretics for 6% and spironolactone for 1% (37).

Thiazide diuretics usually act by inhibiting reabsorption of Na+ and Cl- from the distal convoluted tubule by blocking the thiazide sensitive Na+/Cl- co transporter (38). They therefore inhibit electrolyte transport in the diluting segment and may impair urinary dilution in some susceptible groups. The risk factors predisposing to thiazide induced hyponatremia are old age, female sex, reduced body masses and concurrent use of other medications that impair water excretion (37,39,40).

Hyponatremia is usually induced within 2 weeks of initiating the thiazide diuretic, but it can occur any time during thiazide therapy when subsequent contributory factors are complicated such as reduction in renal function with aging, ingestion of other drugs that affect free water clearance (40).

There have been several relevant studies on diuretics and hyponatremia, despite this and years of clinical experience exact mechanism and optimal treatment of diuretics induced hyponatremia remains unclear. Proposed mechanisms include (i) Stimulation of AVP release secondary to diuretic induced volume contraction (ii) decrease in GFR from intravascular volume contraction (iii) Inhibition of urinary dilution capacity due to interference with Na+ absorption in the distal segment (iv) hypokalemia induced intracellular shift of Na+ (41).

2.3 Types of hyponatremia

The aetiology of hyponatremia can be categorized pathophysiologically in three primary ways, based on the patient's plasma osmolality.

2.3.1 Hypotonic hyponatremia

This is by far the most common type, and is often used interchangeably with "hyponatremia." Hypotonic hyponatremia is categorized in 3 ways based on the patient's blood volume status (19, 42). Each category represents a different underlying reason for the increase in AVP that led to the water retention and hence hyponatremia.

2.3.1.1 Hypervolemic hyponatremia

Wherein there is decreased effective circulating volume even though total body volume is increased (by the presence of oedema). The decreased effective circulating volume stimulates the release of AVP, which in turn leads to water retention. Hypervolemic hyponatremia is most commonly the result of congestive heart failure, liver failure, or kidney disease (19,43).

2.3.1.2 Euvolemic hyponatremia

Wherein the increase in AVP is secondary to either physiologic but excessive AVP release (as occurs with nausea or severe pain) or is due to inappropriate and non-physiologic secretion of AVP, i.e. syndrome of inappropriate anti-diuretic hormone hyper secretion(SIADH), hypothyroidism, adrenal insufficiency or extreme psychogenic polydipsia (19,42,43).

2.3.1.3 Hypovolemic hyponatremia

Wherein AVP secretion is stimulated by volume depletion (19).

2.3.2 Hypertonic hyponatremia

This is caused by resorption of water drawn by osmoles such as glucose (hyperglycemia or diabetes) or mannitol (19,43).

2.3.3 Isotonic hyponatremia

More commonly called "pseudohyponatremia," is caused by laboratory error due to hypertriglyceridemia (most common) or hyperparaproteinemia (19).

2.4 Management of hyponatremia in heart failure

Hyponatremia in heart failure is associated with increased morbidity and mortality, emphasizing the importance of sufficient assessment and treatment of this electrolyte imbalance in patients with heart failure. Management of hyponatremia in heart failure requires a multifaceted approach including optimization of cardiac function. This includes the prevention of fluid overload and neurohormonal blockade, preservation of renal function and maintenance of appropriate fluid intake.

In the setting of acute symptomatic hyponatremia serum sodium concentrations decrease rapidly resulting in appearance of neurological symptoms (12). These neurological symptoms result from brain oedema that results from fluid shifts from the hypotonic extracellular fluid into the more hypertonic brain (19). In the setting of acute symptomatic hyponatremia with neurological symptoms immediate treatment is required to reduce the risk of neurological complications (19,44). The proposed treatment for symptomatic hyponatremia is the infusion of hypertonic saline to increase serum sodium by 1-2 mEq/L per hour until symptoms subside (45).

It has also been shown that infusion of hypertonic saline combined with high dose diuretics was associated with increased in serum sodium level and a potential improvement in outcomes in heart failure patients (46). The combination of furosemide and hypertonic saline increased serum sodium levels and decreased length of stay and re-admissions compared with furosemide infusion alone (47).

In patients with chronic hyponatremia, the rate of correction of sodium level should not exceed the rate of 8 mEq/L any 24 hour period (48,49). Rapid correction increase the danger of central pontine myelinolysis (50, 51).

Therefore current treatment options for hyponatremia in heart failure therefore involve a combination of many methods such as hypertonic saline, loop diuretics, fluid restriction, and other pharmacologic agents, such as demeclocycline, lithium carbonate and urea and the novel agents AVP receptor antagonists (52).

2.4.1 Optimization of Cardiac Function

A basic view of managing hyponatremia in HF is to ensure adequate cardiac output. This reduces the stimulation of baroreceptor and lessens the activation of the SNS and RAAS resulting in less renal avidity for Na+ and water and lower levels of AVP.

Inhibition of the SNS and RAAS with β-blockers and ACEI or ARB remains the foundation of chronic HF management. These medications halt the maladaptive cycle of neurohormonal activation and through various mechanisms lead to improvement of cardiac function (53). These agents also lead to a reduction in left ventricular after load facilitating an improvement in cardiac output. Furthermore, the blockade of the aldosterone action with aldosterone antagonists like spironolactone or eplerenone decreases hospitalizations and mortality in patients with NYHA class 3 and 4 of HF (54,55). In patients with acute decompensated HF, after load reduction with ACEI ,nitrates and utilization of positive inotropic agents may be used to improve cardiac output (56) thus increasing Na+ levels in hyponatremic patients.

Diuretics remain a mainstay of HF treatment and have complex effects on serum Na+ levels. Increasing Na+ and water loss can ease congestive symptoms and, especially in combination with after load reduction and increased inotropy, can improve cardiac output in the volume-overloaded patient (56). Loop diuretics are preferred because they increase electrolyte-free water clearance (39).

Loop diuretics, or in combination with thiazide diuretics are used to achieve this and often can cause increase in Na+ levels in hyponatremic patients. It is imperative to note, however, that excessive diuresis leads to hypovolemia, activation of the SNS and RAAS, and decreased renal function. This effect can worsen cardiac function and lead to impaired renal Na+ and water handling resulting in hyponatremia from increased AVP release (57).

In addition, a single bolus of furosemide has been associated with an increase in plasma renin activity, norepinephrine, and AVP leading to increased left ventricular filling pressure and decreased stroke volume (58). This response to furosemide is potentially harmful to the HF patient.

Diuretic use has been linked with increased mortality in both chronic and acute exacerbations of HF. Chronic diuretic use was associated with increased long term mortality and hospitalizations

in a wide spectrum of ambulatory chronic systolic and diastolic heart failure (59,60). It is difficult, however, to outline a cause and effect relationship, and despite a lack of evidence for their effectiveness, diuretics are expected to remain an important component of HF management in the projected future.

It has also been shown that the addition of loop diuretics to ACEI reversed hyponatremia in heart failure patients (61).

Due to the complex physiology of HF, the effect of loop diuretics on serum Na+ can be difficult to accurately predict thus making frequent monitoring of serum Na+ very important. In addition, non potassium sparing diuretics may lead to considerable hypokalemia, hypomagnesaemia, and decreased renal function. It is, therefore, sensible to ensure sufficient monitoring of these parameters when using these agents.

2.4.2 Preservation of Renal Function

Renal dysfunction causes a decreased capacity for Na+ and water excretion. This causes an increased risk of developing hyponatremia. Therefore maintaining normal renal function including blood pressure control, avoiding excessive diuresis and avoiding the use of nephrotoxic agents minimizes the risk of hyponatremia. In situations where renal function cannot maintain appropriate Na+ and water balance, renal replacement therapy can be used to maintain normal Na+ levels.

2.4.3 Maintenance of Appropriate Fluid Intake

Due to the high levels of circulating AVP, HF patients usually have an inadequate capacity to excrete excess dietary free water. This necessitates that HF patients with hyponatremia should limit dietary water intake. Fluid is restricted to amounts less than 800-1000mL/day to achieve a negative water balance (45). The degree of limitation necessary will be patient specific and dictated by the degree of neurohormonal activation in each patient. Frequent monitoring will help ensure an appropriate rise in serum Na+ in response to the intervention.

2.4.4 Vasopressin Antagonists

Vasopressin plays a physiological role in the regulation of blood pressure, fluid volume and serum osmolality (62).

AVP plays a key role in free water retention and the development of hyponatremia in HF patients, antagonism of AVP action would seem like a prudent therapeutic option in hyponatremic HF patients. Other actions of vasopressin include vasoconstriction and cardiomyocyte hypertrophy therefore blocking its actions may have further favourable effects in HF (22).

Vasopressin receptor antagonists also referred to as aquaretics are a novel class of orally active drugs that are targeted to inhibit one or more of the distinct vasopressin receptors, namely V1a responsible for vasoconstriction, V1b responsible for release of ACTH and V2 receptors involved in inhibition of free water reabsorption in the kidney (62).

In patients with decompensated heart failure and fluid overload, selective V2 (Lixivaptan,Satavaptan and tolvaptan) and non selective V1a/V2-receptor blockers like conivaptan have been shown to be superior to diuretics in fluid overloaded patients as they allow a faster weight loss and rapid symptomatic improvement i.e. dyspnoea without accompanying solute diuresis (63).

Although to date no studies have shown a reduction in mortality with long term use of the vasopressor antagonists in HF to date, there is significant benefit on dyspnoea, oedema, body weight, serum sodium and preservation of renal function. These agents also have an overall good safety profile are defined as potentially useful agents for treating patients with exacerbation of heart failure (14).

The precise role of vasopressin antagonists in the management of hyponatremic HF patients remains unclear. It is important to note that in all of the aforementioned studies, vasopressin antagonists have been used in combination with usual HF treatment (including diuretics), and have not been studied as a replacement for loop diuretics.

2.5 Epidemiology of Hyponatremia in heart failure

It is not surprising that hyponatremia is very common in heart failure due to the number of neurohormonal changes in this population. Sodium and water retention decreased GFR from the activation of the RAAS and SNS in the background of increased AVP levels may lead to hyponatremia. About 18-27% of all the patients admitted with heart failure will have hyponatremia (64–67).

Hyponatremia is not only common but it is also a strong marker of increased morbidity and mortality in heart failure patients.

In USA Asim Mohammed et al, in The International Collaborative of NT-proBNP Study studied 628 patients presenting to the emergency department with acutely decompensated heart failure. Hyponatremia was diagnosed in 24% of the patients. A comparison was made between those with hyponatremia and those with normal Na+ levels and it was found that hyponatremic patients were more prone to have severe symptoms, to be anaemic and to have higher amino-terminal pro B-type natriuretic peptide (NT-proBNP) concentrations ($P< 0.05$) (68).

In a Romanian study, Diaconu and Bartos conducted a study on 434 patients admitted with heart failure and recorded serum Na+ at admission and several times during the hospital stay and at discharge. Hyponatremia was present in 127 patients (29.26%) of the patients at admission and it persisted during hospitalization in 91 out of 127 patients (71.65%). Patients with persistent hyponatremia had lower systolic blood pressure and received higher doses of diuretics during hospitalization. Hyponatremia was associated with higher in-hospital mortality of 19.78% in those with persistent hyponatremia when compared with normonatremic who had a mortality of 1.48 % (68).

Farooq Ahmad et al in Pakistan conducted a descriptive study on 241 patients with heart failure. It was found that 85 (35.3%) of patients with heart failure had hyponatremia. The overall in-hospital mortality rate was 5.4%. Hyponatremia at admission was associated with a higher in-hospital mortality of 8.2% as compared to 3.8% for those patients with normal serum sodium. ($P=0.23$) The overall length of hospital stay in heart failure was 3.8±2.24 days. The longer mean length of hospital stay 4.1±1.8 days was observed for hyponatremic group compared with 3.7±2.4 days for the normonatremic group ($p=0.009$) (69).

In the COAST Study (Clinical Characteristics and Outcomes in Relation with Serum Sodium levels in Asian Patients Hospitalized with Heart Failure), done in South Korea, Taiwan and China that analyzed about 1470 patients, found a prevalence of 16.8% of hyponatremia. The 12-month mortality was higher in hyponatremic patients (27.9% vs. 14.6%, $p < 0.001$), with hyponatremia being an independent predictor of 12-month mortality (hazard ratio, 1.72; 95% confidence interval, 1.12 to 2.65) (70).

In Tunisia, a retrospective study of 234 patients found hyponatremia in 63 patients (26.9%). The mortality was significantly higher in patients with hyponatremia at 15.87% compared to 4.09% in those with normonatremia (p=0.004) (71).

Lee and Packer analyzed 30 clinical, hemodynamic and biochemical variables and their association with survival in 203 consecutive patients with severe heart failure. The patients were subsequently followed for 6-94 months. Of those parameters, the most important predictor of cardiovascular mortality was pre-treatment serum sodium with hyponatremic patients having a significantly shorter median survival than patients with normal serum Na+ (164 versus 373 days, P=0.006) (72).

Gheorghiade et al, in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), which is a registry involving 259 hospitals, showed that patients with hyponatremia had significantly higher rates of in-hospital and follow-up mortality plus longer hospital stays. After adjusting for differences in multivariate analysis, the risk of in-hospital death increased by 19.5%, the risk of follow up mortality by 10% and the risk of death or rehospitalization by 8% for each 3 mmol decrease in admission serum sodium level below 140 mmol/L (13).

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STUDY	YEAR	SITE	DESIGN	SAMPLE SIZE	PREVALENCE
Chirag et al	2014	USA	Prospective Cohort	2483	13.2%
Ahmad et al	2012	Pakistan	Cross Sectional	241	35.3%
Rawal et al	2012	India	Cross Sectional	650	51.38%
Sonnia et al	2015	Tunisia	Cross Sectional	234	26.9%

CHAPTER 3

3.0 Study Justification

Hyponatremia has been shown to be a common electrolyte abnormality which is frequently overlooked in heart failure patients. It is a marker of severe illness associated with adverse short term outcomes. Europe, Asia and the Americas have highlighted the importance and the burden of hyponatremia in heart failure. There is a distinct genetic and environmental difference between our local setup and the other geographical locations. Therefore, it was important to fill in the knowledge gap in our set up concerning hyponatremia in heart failure.

CHAPTER 4

4.0 Research Question

What is the prevalence of hyponatremia in patients admitted with heart failure at the Kenyatta National Hospital?

4.1 Objectives

Primary Objective

1) To establish the prevalence of hyponatremia in patients with heart failure admitted at The KNH.

Secondary Objectives

1) To determine the two week outcomes in patients admitted with hyponatremia in heart failure at the KNH.
2) To relate the level of sodium to the functional status of patients with heart failure.

CHAPTER 5

5.0 METHODOLOGY

5.1 Study Design

This was a prospective, observational cohort study.

5.2 Study Site

The study was conducted in the medical wards of Kenyatta National Hospital. The KNH is a teaching and referral hospital located within an urban environment in Nairobi. The main catchment population is, however mainly from Nairobi, Central and Eastern regions of the country. The KNH has 7 medical wards with an average of 70 patients.

5.3 Study Population

Patients above 13 years of age admitted with heart failure in the medical wards at the KNH.

5.4 Case Definitions

All patients fulfilling the Modified Framingham Clinical Criteria of heart failure and were admitted in the medical wards at KNH. (Appendix 4)

5.5 Inclusion Criteria

Thirteen years or more of age.

Admission into the medical wards with heart failure.

Signed informed consent or assent for patients below 18 years.

5.6 Exclusion Criteria

Patients who had previous known chronic kidney disease with fluid overload.

Patients who had previous known liver disease with fluid overload.

5.7 Functional Status Assessment

Assessment of the patient's functional status was assessed using the New York Heart Association Criteria (Appendix 5).

5.8 Sample Size Calculation

According to KNH data from hospital records (2010-2014), an estimated number of 500 heart failure patients are admitted annually. This study was expected to run for a maximum of 3 months hence the accessible population was about 125 participants. A representative sample was drawn from the population in the period and the sample size calculation was obtained using the formula for finite population (Daniel, 1999). The calculation was as follows:

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1) + Z^2P(1-P)}$$

Where

n' = sample size with finite population correction,

N = size of the target population = 125

Z = Z statistic for 95% level of confidence = 1.96

P = Estimated proportion of hyponatremia= 26.9% (Sonia et al, 2015)

d = margin of error = 5%

$$= \frac{125 \times 1.96^2 \times 0.269 \times 0.731}{0.05^2 (125-1) + 1.96^2 \times 0.353 \times 0.731}$$

= **89 heart failure Patients**

A minimum of 89 heart failure patients was needed to estimate prevalence within margin of error or 5% at 95% confidence interval.

5.9 Sampling Method

The patients were sampled consecutively on a daily basis from the wards until the sample size was obtained.

5.10 Screening and Recruitment

The Principal Investigator and a trained registered clinical officer as a study assistant reviewed the admission records of patients admitted to the medical wards the previous day with heart failure. The patients who met the inclusion criteria according to the Modified Framingham's criteria were approached about participating in the study and the details of the study were explained to them in order to obtain informed consent from them. A study explanation was given to them to read through and any questions or concerns raised were addressed. Once patients understood the study explanation and were willing to participate in the study, they were requested to sign the consent form. A thorough, targeted history was taken, physical examination carried out and investigations undertaken in those that signed the consent by the principal investigator. Those patients who declined consent were not discriminated against in any way, but were left to undergo routine ward evaluation and management.

5.11 Data Collection

The principal investigator and research assistant collected data daily from the admitting ward. Once written consent was obtained, 2 mls of blood was drawn from the patient's forearm and collected aseptically in plain vaccutainers. Laboratory evaluation of serum sodium was done within 24hrs of admission. The patients were then followed up daily noting in-hospital mortality, prolonged length of hospital stay beyond 2 weeks and discharge from the wards. The data was then recorded in a study proforma and entered in data entry sheets.

5.12 Laboratory Methods

Serum sodium levels were done in the renal laboratory using a well calibrated BioLis 50i Superior machine, which is validated for precision, accuracy, linearity, sensitivity and specificity in the measurement of electrolytes.

5.13 Quality Control

The research assistant underwent training by the principle investigator on how to fill the transcription form to ensure standardization and minimize pre analytical errors. Aseptic

technique was used for specimen collection; proper labelling, preparation and storage were followed strictly to minimize pre analytical sources of error. The laboratory calibrates all equipment according to the manufacturer's specifications. Commercial control materials were used to validate calibrations. These were included in all analytical runs. Results were only accepted if the control values were within the expected ranges. The reference ranges were between 135-145 mmol/L.

5.14 Study Variables

Independent Variables

These include age, sex, cause of heart failure, and heart failure medication in use at admission, NYHA functional status.

Dependent Variables

Serum Sodium

- Hyponatremia is defined as serum Sodium < 135 mmol/L
- Normonatremia is defined as serum Sodium 135-145 mmol/L
- Hypernatremia is defined as serum Sodium >145 mmol/L

Outcome at 2 weeks

Discharged: Patient who is alive at day 14 either in the ward or at home, confirmed by contacting patient or relative.

Deceased: Those who had died by day 14.

Prolonged stay: Patient who was alive by day 14 in the wards with no physician documented discharge.

5.15 Data Management

Data prospectively recorded into the study proforma was entered into computerized data entry sheets. Cleaning and verification was done on a weekly basis to ensure validation and completeness of the information. Data analysis was conducted using SPSS version 21.0 software. Patients were described by summarizing their socio-demographic and clinical characteristics using percentages for categorical variables and means/medians for continuous variables.

Prevalence of hyponatremia was calculated as a percentage of patients with sodium <135 mmol/L and presented with 95% confidence interval. Short term outcomes of patients with hyponatremia were analyzed and presented as patient dead, discharged or still admitted in the wards using percentages. NHYA functional class and short-term outcomes were associated with hyponatremia using Chi square test of associations. Odds ratios were calculated and presented as estimates of relative risk associated with hyponatremia. All statistical tests were interpreted at 5% level of significance (p value less or equal to 0.05). Study findings were presented in tables and graphs.

5.16 Ethical Consideration

Only patients who gave informed consent were recruited into the study after signing the consent form. The study was undertaken after approval by the department of clinical medicine and therapeutics, University of Nairobi and the KNH/UON joint ethics committee.

1. Patients were free to withdraw from the study at any point and were not discriminated against.

2. Patients were recruited on a voluntary basis and those who declined to consent were offered standard hospital care.

3. Confidentiality was maintained by excluding patients' names from the computerized data entry sheets and storing the proforma in a secure location.

4. Only blood samples intended for the study were drawn. Samples taken were discarded after analysis.

5.The results of the laboratory measurements were communicated back to the patient and inserted in the patient's file for use by the medical team managing the patient. In those with severe hyponatremia the attending physicians were contacted immediately for correction.

6. Patients were managed using standard hospital protocol.

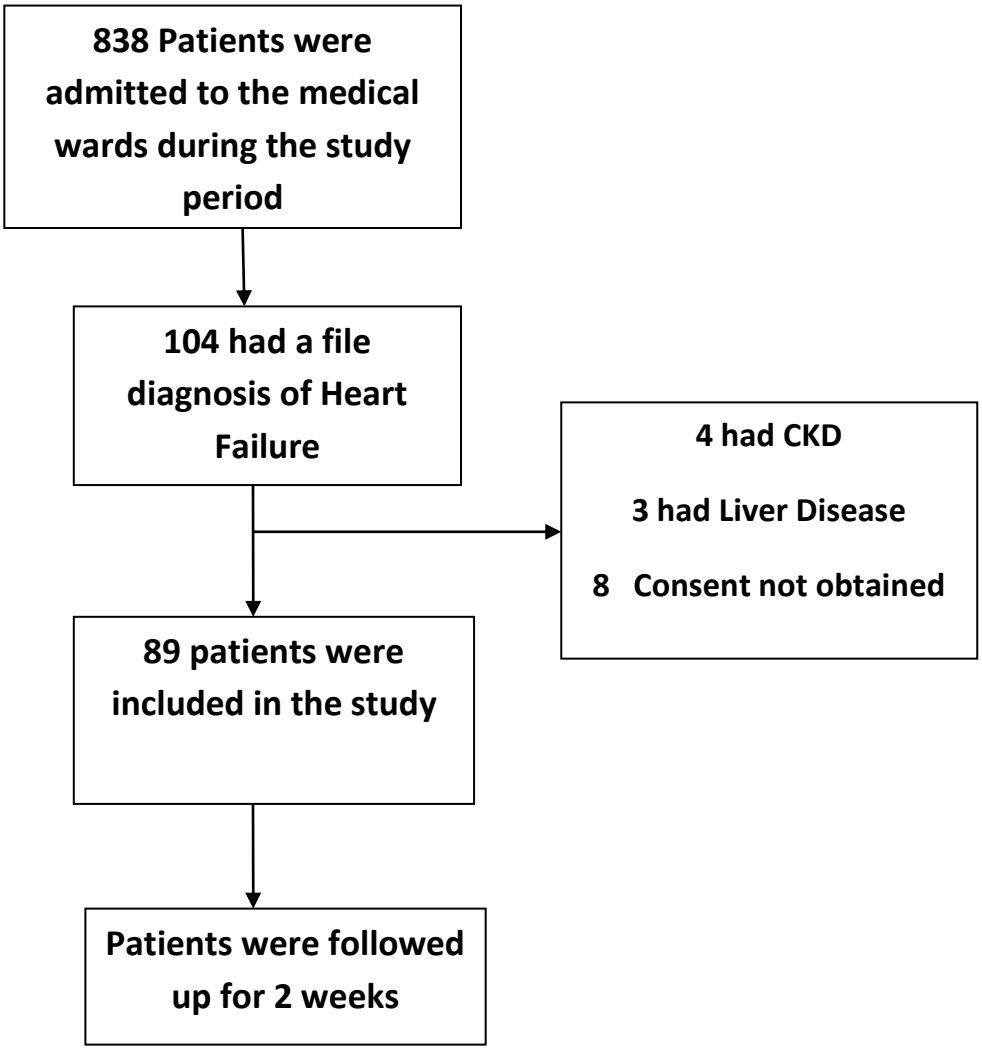
7. Data collected during the study, both hard and soft were kept confidential and on completion of the study were handed over to the department of Clinical Medicine and Therapeutics to be made available for subsequent follow up on this cohort of patients.

CHAPTER 6

6.0 Results

The study was conducted over a period of two and a half months, from the 15th of December 2015 to the 27th of February 2016. During this time one hundred and four patients were screened for heart failure in the medical wards using the modified Framingham's criteria. Out of these seven did not meet the inclusion criteria and were excluded. Ninety seven satisfied the criteria for heart failure. Eight patients did not consent to the study. Eighty nine patients were recruited into the study.

Figure 1: Recruitment Flow Chart



6.1 Demographic Profile

The mean age of the study population was 51.6 (SD±18.8) years. Most of the patients in the study were above 40 years of age (78.7%). There was a slight male preponderance at a ratio of 1.2:1 (Table 1)

Table 1: Demographic profile

Age (yrs)	
Mean(SD)	51.6(18.8)
Min-Max	14-86
Age Distribution 10-19 20-29 30-39 40 and above	**Frequency (%) n=89** 7 (6.9) 6 (6.7) 6 (6.7) 70 (78.7)
Variable	**Frequency (%) n=89**
Gender	
Male	48(53.9)
Female	41(46.1)

6.2 Clinical Profiles

The aetiology of heart failure in most of the patients studied was hypertensive heart disease which comprised 42.7% of the study population.Cardiomyopathies comprised 27.0% of the cause of heart failure in this study population. 21.3% of the patients studied had rheumatic heart disease (Table 2).

Table 2: Aetiology of Heart Failure at admission

Variable	
Diagnosis	**Frequency (%) (n=89)**
Hypertensive Heart Disease	38(42.7)
Cardiomyopathies	24(27.0)
Rheumatic Heart Disease	19(21.3)
Cor Pulmonale	4(4.5)
Ischaemic Heart Disease	3(3.4)
Congenital Heart Disease	1(1.1)

6.3 Prevalence of hyponatremia in heart failure

Analysis of sodium revealed that mean sodium level was 128.2 ±8.1 mmol/L. The range was between 106 and 153. The highest proportion of heart failure patients had hyponatremia 79.8% (95% CI 71.9-87.6) while 1.1% (95% CI 0-3.4) had hypernatremia (Table 3).

Table 3: Prevalence of hyponatremia

Variable	**Frequency (%)**	**95% CI**
Sodium levels		
Hyponatremia	71 (79.8)	71.9-87.6
Normonatremia	17 (19.1)	11.2-27.0
Hypernatremia	1 (1.1)	0-3.4

6.4 Heart Failure Medication and Functional status at admission

Of all patients, 84.3% were on loop diuretics, 48.3 % on ACE/ARB, 38.2 % were on beta blockers and 15.7% were on aldosterone antagonists. 6.7% of the patients were on thiazide diuretics.On admission 49.5% and 44.9% of the patients were in New York Heart Association Class III and IV, respectively comprising 94.4% of the study population. There were no patients admitted in NYHA class I and only 5.6% were in NYHA class II (Table 4).

Table 4: Heart Failure Medication and Functional status at admission

Medication at Admission	**No. (%)**
ACE/ARB	43(48.3)
Aldosterone antagonists	14(15.7)
B-Blockers	34(38.2)
Loop Diuretics	75(84.3)
Thiazide Diuretics	6(6.7)
Loop Diuretic + Thiazide	4(4.5)
Loop Diuretic + Aldosterone antagonists	13(14.6)
Digoxin	25(28.1)
No heart failure medication at admission	13(14.6)
Functional Status	**Frequency (%) n=89**
NYHA II	5(5.6)
NYHA III	40(44.9)
NYHA IV	44(49.5)

6.5 Two week outcome in patients admitted with hyponatremia in heart failure

Of all those admitted with heart failure with hyponatremia 42.2% were still admitted and undergoing treatment at the end of the 2 weeks. 11.3% had succumbed by the lapse of the two weeks while 46.5% had been discharged**.** (Table 5)

Table 5: Two week outcome of hyponatremic patients

Status at 2 weeks post admission	**Frequency (%) n = 71**
Prolonged stay	**30(42.2%)**
Deceased	**8(11.3%)**
Discharged	**33(46.5%)**

6.6 Associations between NYHA class, short term outcomes and hyponatremia

Patients, in higher NYHA functional class were more likely to be hyponatremic. Presence or absence of hyponatremia did not affect the outcomes in a statistically significant way. The trends, however, suggest worse outcomes in the hyponatremia patients. (Table 6)

Table 6:Association between NYHA class, short-term outcomes and hyponatremia

Variable	**Hyponatremia (%)**	**Normal (%)**	**OR (95% CI)**	**P value**
Functional status				
NYHA Class II	4 (80.0)	1 (20.0)	1.0	
NYHA Class III	27 (69.2)	12 (30.8)	0.6 (0.1-5.6)	0.623
NYHA Class IV	40 (90.9)	4 (9.1)	2.5 (0.2-28.1)	0.458
Outcome				
Prolonged stay	30 (88.2)	4 (11.8)	2.0 (0.6-7.3)	0.272
Deceased	8 (66.7)	4 (33.3)	0.5 (0.1-2.2)	0.399
Discharged	33 (78.6)	9 (21.4)	1.0	

CHAPTER 7

7.0 Discussion

A total of 89 patients with heart failure aged between 14-86 years old, with a mean age of 51.6 years were included in this study during the study period. 78.7% of these patients were aged 40 years and above. Of these patients, 53.9% were males. Oyoo et al in 1995 in the same setting found 48.9% patients to be male (3). Parmar et al in KNH in 2009 also found a higher female preponderance at 59.1% (75). The explanation on this change to a slightly higher male preponderance could be due to the fact that in this study hypertensive heart disease was the commonest aetiology of heart failure as opposed to rheumatic heart disease in the above previous studies. The World Health statistics 2016, showed a higher prevalence of hypertension among males worldwide (76). Another plausible explanation could be due to better control of heart disease among females who are traditionally known to have better health seeking behaviour leading to fewer complications like heart failure. To date, however, research on sex differences in heart failure has had a limited impact on practice. Inconsistent findings in the literature have left clinicians confused about the implications for clinical care. A majority of previous studies have found that men with heart failure have a worse survival, but other studies have been neutral and at least one study suggested that women have a worse outcome (82).

49.5 % of patients admitted in heart failure were in NYHA IV while 44.9% were in NYHA III. Few patients admitted were at NYHA II at 5.6% while no patients was found at NYHA I. Kamau et al in 2009 in KNH found 60.5% of the patients were admitted at NYHA IV while 37.2% were in NYHA III while Oyoo et al in 1995 found 94.5% of the patients were NYHA class III and IV (5). This shows that a majority of patients admitted in heart failure are in the latter stages of the disease and the state has remained so in the last two decades. This could be explained by the fact that Kenyatta National Hospital is a referral hospital serving a large catchment area with resource constraints, therefore, most of the patients admitted tend to have more advanced symptoms necessitating in-hospital care. There may also be a tendency to admit only the critically ill patients with the less ill cases though deserving admission to be sent home due to limited bed

capacity. It may also be a reflection of health seeking behaviour such that patients present when their functional capacity is severely compromised.

Hypertensive heart disease was the cause of heart failure in 42.7% of the patients in this study. This made it the most common cause of heart failure in patients admitted in KNH during the study period. This is different compared to what Oyoo et al found in 1995 whereby rheumatic heart disease was the leading cause of heart failure. However, our finding in this study was in keeping with a study done earlier in 1969 in Dar-es-Salaam by Nhonoli that had shown hypertension was the most common cause of heart failure (73). This change could be due to effects of increasing urbanization with an uptake of a western lifestyle. This has led to an increase in lifestyle diseases like hypertension in our population.

The prevalence of hyponatremia was found to be at 79.8%. The mean sodium level was 128.2 mmol/L. Of these patients with hyponatremia, a majority at 40.9% had profound hyponatremia of less than 125 mmol/L while 36.6% had mild hyponatremia of between 130 and 134 mmol/L.

Reports of the prevalence of hyponatremia in heart failure ranges from 10-64% (75).The plausible explanation to this is the difference in baseline characteristics of the patients in heart failure. In our study, we studied in-patients who had decompensated heart failure necessitating admission in hospital.

This high prevalence of hyponatremia in heart failure is multifactorial. It can be explained by the fact that 94.4% of the patients in our study were in NYHA functional class 3 and 4 which denotes a moderate and severe stage of the disease.This is accompanied by an over activation of the the RAAS and the SNS that occurs in severe heart failure with a low cardiac output.This leads to non osmotic release of AVP which ultimately leads to fluid retention and dilutional hyponatremia.Frederik et al demonstrated that in acute decompensated heart failure denoted by a higher NYHA there is a sympathetic overdrive and angiotensin II release due to a decrease in effective circulatory volume that fuels non osmotic release of AVP that leads to fluid retention and dilutional hyponatremia (78).

Diuretics were in use by a majority of patients in our study at admission. Loop diuretics were in use by 84.3% of the patients at admission, while thiazide diuretics and aldosterone antagonists were in use by 6.7% and 15.7% of the patients at the time of admission respectively. These

findings were expected as the patients admitted had decompensated heart failure and were fluid overloaded. About 19.1% were on combined diuretics. This is denoted as intensive diuretic therapy and it is associated with high incidence of hyponatremia. Sonnenblick et al showed that diuretics contribute to hyponatremia in heart failure more so when used in combination and this may have contributed to the high prevalence of hyponatremia in our study population (37).

48.3% of our study population was on ACEI/ARB, while 38.2% were on beta blockers with 14.6% of the study subjects being on no heart failure medication at admission. This demonstrates poor control of heart failure. Pérez-Villa et al demonstrated that low use of ACEI /ARB and beta-blockers leads to a persistence of neurohormonal activation with high levels of renin, angiotensin II and norepinephrine with dysfunction of myocardial activity with attendant complications such as hyponatremia (78).

Our study population was captured in an acute hospital setup. Hyponatremia is common in acutely ill patients regardless of the aetiology. It occurs in 15-30% of such patients (79). Verbrugge et al demonstrated this phenomenon of transient hyponatremia in patients with acute decompensated heart failure where it occurred in more than 50% in an acute hospital set up in the post hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) and Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE AHF) (76).

Our study compares favourably to what Rawal et al found in a similar study in India. He studied a cohort of patients with decompensated heart failure who were mostly in NYHA 3 and 4 functional status and found a prevalence of hyponatremia at 51.38%. Of these, 57.14% had profound hyponatremia of less than 125 mmol/L. In his study there was a high use of diuretics,with two diuretic molecules co-administered in 39.7% of the participants (80).

In a different study by Bavishi et al in the USA, they found a lower prevalence of 13.2% in ambulatory heart failure patients in the community who were mostly in NYHA functional class 2. However the participants in that study had higher use of ACE/ARB and beta-blockers compared to our study (81).

Hyponatremic patients have been shown to have a poorer outcome with regards to mortality and morbidity (68, 69). The overall in-hospital mortality of the patients with heart failure during the

2 weeks follow-up was 13.5%. In those patients who had hyponatremia at admission, 11.3% of them died. Of those that died 66.7% had hyponatremia at admission. There was however no association between level of sodium at admission and mortality in the two week study period. The majority (88.2%) of those with a prolonged stay beyond 2 weeks had hyponatremia at admission compared to those with normonatremia, but it was not statistically significant.

This mortality was higher than the 7.3% that was reported by Hamdi et al in Tunisia over the 6 month follow up period (71). This could be explained by the fact that the patients in that study were followed up in a specialized cardiology unit.

Farooq et al in Pakistan found an overall in-hospital mortality of 5.4% over a 6 month period. In his study, 8.2% of the patients with hyponatremia died compared to 3.8% of those with normal sodium levels. This was however not statistically significant similar to our study (69).

There was a trend towards hyponatremia in those with NYHA functional class 3 and 4 thou there was no statistically significant association found between the level of sodium and the NYHA functional class. The study was however not adequately powered to test the association because of the limited number of patients and the short duration of follow-up.
The significance of hyponatremia in heart failure is that it is common and more so in patients with decompensated heart failure and it is associated with a poorer outcome, especially in the long term.

Conclusion

This study shows a high prevalence of hyponatremia in patients admitted with heart failure at the KNH compared to what is seen in other parts of the world. Most of the patients have moderate and severe heart failure at admission. Presence or absence of hyponatremia does not seem to affect the two week outcomes in a statistically significant way, the trend suggested higher mortality and prolonged length of hospital stay beyond two weeks. There is no statistically significant relationship between hyponatremia and NYHA functional status; though there was an inclination towards hyponatremia in the patients with severe heart failure.

7.2 Recommendations

1. We recommend regular monitoring of sodium levels in patients admitted with heart failure.

2. Long term follow up studies with a larger sample size with frequent monitoring of sodium in heart failure should be conducted to help answer the question of impact of hyponatremia.

7.3 Study Limitations

1) This was a single center study, done in a referral centre with a restricted sample size and limited time, therefore the results may not be generalizable to our Kenyan population.

2) The sodium level was taken only at admission and a repeat was not done to determine if there was persistence of the hyponatremia and what effect it would have on the outcome.

3) This study could not elucidate the exact cause of the hyponatremia and therefore no conclusion on the appropriate intervention could be made.

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Appendix 1: Statement of Information and consent form

Introduction

I, **Dr. Edgar Munene Karanga**,a postgraduate student in the department of Clinical Medicine and Therapeutics of the University Of Nairobi am conducting a study on the:-

Prevalence of hyponatremia in patients admitted with heart failure at the Kenyatta National Hospital .

Purpose of the study

We want to find out the level of sodium in patients admitted with heart failure at Kenyatta National hospital. This will enable us to treat people with heart failure better.

Basis of participation

Your participation will be purely voluntary.You are free to withdraw at any time during the course of the study period.Your refusal to participate or withdrawal at any time during the study period will not in any way affect the quality of your treatment.

Confidentiality

All information obtained in the study will be treated with utmost confidentiality.

I shall NOT use your name in any of my reports.

Benefits

The results of this study may be published in a medical book or journal or for teaching purposes and will be given to the community for better understanding of this topic. Once the results are ready, we will inform your doctor, who will then inform you about your sodium levels and advice you accordingly.

Risks and discomfort

The process of drawing blood may be slightly painful but only for a few seconds. Some of the questions asked may be personal but privacy and confidentiality will be assured at all time.

Request for information

You may ask more questions about the study at any time or at this moment.You will be informed of any significant findings discovered during or after the study.

Cost

Participating in this study will not have any added cost to the patient.

Having read this consent form,all my questions have been answered,my signature below indicates my willingness to participate in this study and my authorization to use and share with others.

I……..the(Patient/Guardian)
of……after reading and having the study purpose explained to me by Dr.Edgar M. Karanga,do hereby give informed consent to participate in the study :**Prevalence of hyponatremia in patients admitted with heart failure at the Kenyatta National Hospital.**

Signed…….. Date…….

Thumb Print…….. Date……..

I confirm that I have explained to the patient the above statement.

Signature of questionnaire Investigator (Dr.Edgar M. Karanga)…….....

Dr. Edgar Munene Karanga

Phone No. 0723176481

Assent Form (AGE 13-17)

Introduction

My name is **Dr. Edgar Munene Karanga**. I am a post graduate student in the department of Internal Medicine at the University of Nairobi.

I am conducting a study on the :-

Prevalence of hyponatremia and in patients admitted with heart failure at the Kenyatta National Hospital .

Purpose of the study

We want to find out the level of sodium in patients admitted with heart failure at Kenyatta National hospital and how it influences the course of the disease. This will enable us to treat people with heart failure better.

Benefits

The information we obtain will be shared with your doctor to help in better treatment of your illness.

Confidentiality

When we complete the study we will write a report about what we have learned. Your name will not be included in the report.

Risks and discomfort

The process of drawing blood may be slightly painful but only for a few seconds. Some of the questions asked may be personal but privacy and confidentiality will be assured at all time. You will also be examined before starting the study.

Request for information

You may ask more questions about the study at any time or at this moment.You will be informed of any significant findings discovered during or after the study.

Cost

Participating in this study will not have any added cost to you.

Voluntary Participation

You do not have to be in the study if you do not want to be in it. After we begin the study and you do not want to take part in it any further it is fine. We have informed your parents/guardian about the study.

If you agree to take part in the study, please sign your name.

Name of the Participant_____ Date_____

Sign your name _____

I confirm that I have explained the details of the research to the participant.

Researcher's Name _____ Date_____

Signature of Researcher_____

Principal Investigator

Dr. Edgar Munene Karanga

Phone No. 0723176481

Appendix 2: Investigator's Statement

I the investigator have educated the research participant on the intention and applications of this study.

Signed…… Date……

For further enquiries during the course of the study, contact the following:

Principal Investigator

Dr. Edgar Munene Karanga

Mobile: +254 723 176 481

Lead Supervisor

Dr. Emma. Karari

DCMT/ UON

Mobile: +254 722 847 345

The Secretary

KNH/UON Ethics and Review Committee

Tel: 2726300, Ext: 4410

Appendix 3: Study Proforma

Patient Code……

Case No……....

Hospital No……..

Sex Male ☐

Female ☐

Age……..

Date of enrolment ……/……/……

Aetiology of Heart Failure Ischaemic ☐ Hypertensive ☐ Cardiomyopathy ☐

Rheumatic Heart Disease ☐ Congenital Heart Disease ☐

Other ☐

Level of Sodium……mmol/L(135-145)

New York Heart Association Functional Class

Class I ☐

Class II ☐

Class III ☐

Class IV ☐

Medication at Admission

ACE/ARB ☐

β blockers ☐

Aldosterone antagonist ☐

Loop Diuretics ☐

Thiazide Diuretics ☐

Digoxin ☐

Others (Specify) …..……..

OUTCOME at 2 WEEKS

Prolonged stay beyond 2 weeks ☐

Discharged within 2 weeks ☐ Deceased ☐

Appendix 4: Modified Framingham's Criteria Form

Table 1. Modified Framingham Criteria for the Diagnosis of Heart Failure[a]

Major Criteria	Minor Criteria
Paroxysmal nocturnal dyspnea or orthopnea	Bilateral ankle edema
Neck vein distension	Pleural effusion
Crackles/rales (>10 cm from the base of the lung)	Night cough
Acute pulmonary edema	Dyspnea on exertion
S_3 gallop	Hepatomegaly
Weight loss >4.5 kg in response to CHF treatment	Tachycardia >120 bpm
Central venous pressure >16 cm H_2O	Weight loss >4.5 kg caused by heart failure where factors other than treatment of CHF could have contributed to the weight loss
Echocardiographic left ventricular dysfunction	

[a] For diagnosis of heart failure, two major criteria or one major and two minor criteria are needed.
bpm: beats per minute; CHF: congestive heart failure; S_3: ventricular filling murmur.
Source: Reference 9.

REFERENCE VALUES

The reference ranges for sodium will be between 135-145 mmol/L as provided in the BioLis 50i Superior machine manual.

Appendix 5 : New York Heart Association Functinal Classification

Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction)
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue palpitations, dyspnoea or angina pectoris(mild CHF)
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (Moderate CHF)
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (Severe HF)

Appendix 6 : Study Approval Letter

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH-UON ERC
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KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/480

30th November 2015

Dr. Edgar Munene Karanga
Reg. No.H58/69106/2013
Dept.of Clinical Med. & Therapeutics
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Karanga

Revised research proposal: Prevalence of Hyponatremia and Short Term Outcomes in Participants admitted with Heart Failure at the Kenyatta National Hospital (P598/09/2015)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above proposal. The approval periods are 30th November 2015 – 29th November 2016

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH- UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chair, KNH-UoN ERC
The Dean, School of Medicine, UoN
The Chair, Dept. of Clinical Medicine and Therapeutics, UoN
Supervisors: Dr. Emma M. Karari, Prof. Joshua K. Kayima

Protect to Discover

KENYATTA NATIONAL HOSPITAL
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Email: knhadmin@knh.or.ke

Ref: KNH/AD-MED/42B/VOL.1 **Date: 3rd December, 2015**

Dr. Edgar Munene Karanga
Department of Clinical Medicine & Therapeutics
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Karanga

RE: APPROVAL TO CONDUCT STUDY IN KNH, MEDICINE DEPARTMENT

Following approval of your study by the KNH/UoN ERC and completion of the KNH study registration form, permission is hereby granted for you to collect data from Medicine Department to enable you complete your research on study titled: ***"Prevalence of Hyponatremia and short term outcomes in participants admitted with heart failure at the Kenyatta National Hospital".***

Kindly liaise with the Senior Assistant Chief Nurse, Medicine Department for facilitation. By a copy of this letter, the Senior Assistant Chief Nurse, Medicine Department is informed and requested to facilitate.

DR. ANN WAWERU
ASSISTANT DIRECTOR, MEDICINE

Cc. Senior Assistant Chief Nurse, Medicine