PROSPECTIVE OBSERVATIONAL STUDY TO DETERMINE THE CAUSES OF HYPOKALEMIA IN MEDICAL WARDS AND ITS ASSOCIATION WITH OTHER COMORBIDITIES AND DEATH

A dissertation submitted in partial fulfilment of the rules and regulations for MD General Medicine examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai, to be held in April 2016

DECLARATION

This is to declare that this dissertation titled "Prospective Observational study to determine the causes of hypokalemia in medical wards and its association with other comorbidities and death" is my original work done in partial fulfilment of rules and regulations for MD General Medicine examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai to be held in April 2016.

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is a bonafide work done by

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towards the partial fulfilment of rules and regulations for MD General Medicine degree examination of the Tamil Nadu Dr.M.G.R Medical University, to be conducted in April 2016.

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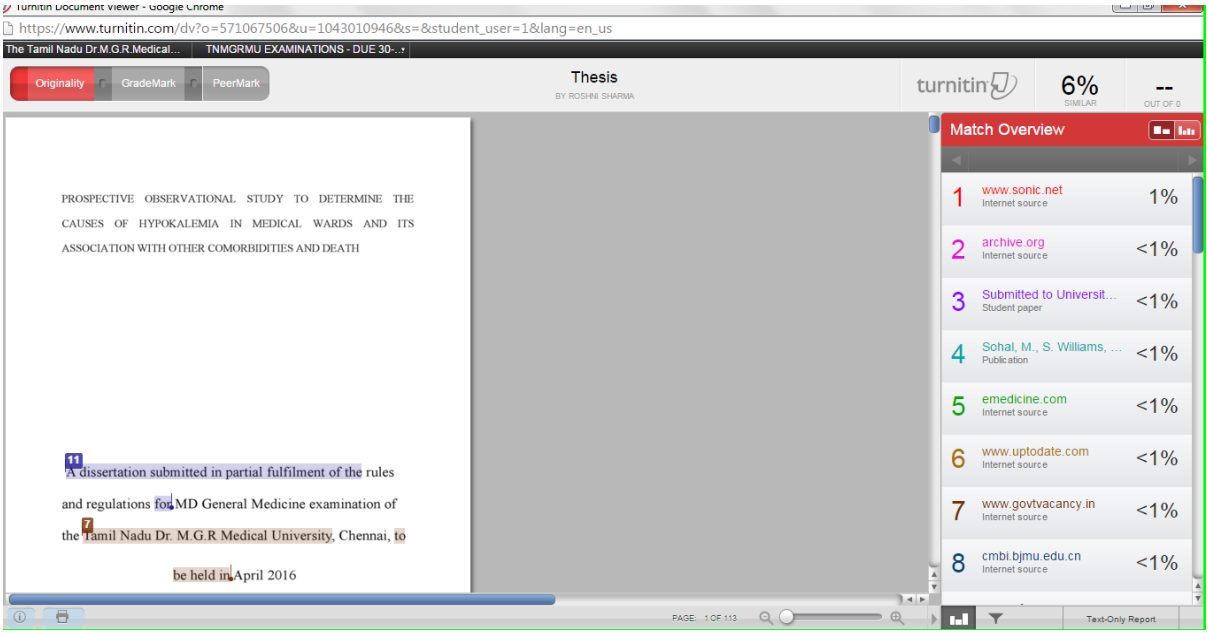

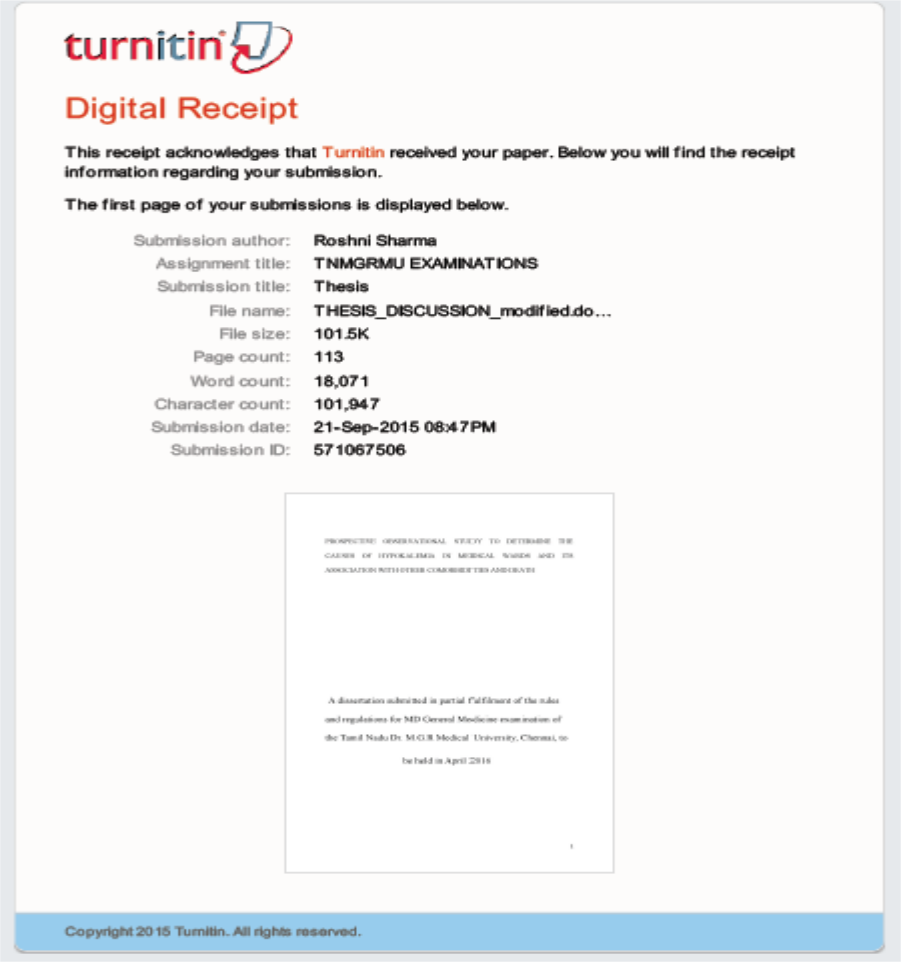

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INTRODUCTION

Hypokalemia is a common clinical problem. It is defined as serum potassium less than 3.5meq per litre. The route through which potassium enters the body is oral and intravenous after which it gets stored mainly in the cells. It is the most abundant cation present in the human body. The total potassium content in the body is about 4,000 meq (1). 98% of this is in the intracellular fluid compartment (2). The extracellular fluid contains only about 60 meq(3). The maximum storage of potassium is in the skeletal muscles (2600 meq)(1).The ratio of the concentration of potassium within the cells to extracellular fluid potassium concentration reflects the resting membrane potential (RMP)(2) which remains constant .The normal level of potassium between cells and body fluids is maintained by the Na-K-ATPase pump located on the cell membrane. Through this pump 3 sodium ions move out of the cells in exchange for 2 potassium ions into the cell. Most of this potassium that enters the cells exits by a potassium channel. Every potassium ion that comes out of this channel carries one positive charge. This maintains most of the RMP. There are two hormones which cause a shift of potassium into the cells. These are insulin and catecholamines. They also bring about the movement of sodium out of the cells; but, by different mechanisms. The action of insulin is through the Na-H-exchanger(4) whereas catecholamines act through the Na-K-ATPase(5). Potassium is excreted from the body through the kidneys. Here, tubular reabsorption occurs in the proximal convulated tubule as well as the loop of henle whereas active secretion occurs in the principal cells of the connecting tubule and cortical collecting tubule. In these areas, sodium is reabsorbed in exchange for potassium. This actively secreted potassium is the one

which gets excreted from the body. The hormone which plays a major role in this process is aldosterone(6,7).

During times of increase is the body's potassium, aldosterone is released. It acts on the principal cells which in turn increases the active secretion of potassium in exchange for sodium leading to normalization of body's potassium level.

There are three ways in which the kidney responds to hypokalemia:

a) Hypokalemia causes a block to the secretion of aldosterone which leads to decreased sodium reabsorption in the distal convulated tubule and hence decreased active secretion of potassium leading to conservation of body's potassium (8,9).
b) Hypokalemia causes stimulation of the release of rennin and angiotensin II. These hormones cause a down regulation of the potassium secreting channels in the distal convulated tubules which in turn leads to decrease in the excretion of potassium(10).
c) Hypokalemia causes activation of H-K-ATPase pump present in the apical membrane of type A intercalated cells, which are located adjacent to the principal cells in the cortical collecting tubules(11). The function of this pump is to take in potassium and secrete hydrogen.

Therefore, the mechanisms by which hypokalemia occur are:

i) Decreased intake
ii) Increased translocation into the cells
iii) Increased excretion (renal, gastrointestinal tract, sweat)

OBJECTIVES

The following are the objectives of this study:

1. To find the proportion of patients with hypokalemia and its causes in adult medical wards
2. The dose and duration of potassium(intravenous or oral or both) required for correction
3. Correlation of hypokalemia with mortality
4. Association of hypokalemia with other comorbidities
5. Association of ECG changes with severity of hypokalemia

LITERATURE REVIEW

DEFINITION

Potassium is an inorganic metal with an atomic weight of 39. It is the most abundant cation in the body. Normal serum potassium is 3.5 to 5.5 meq per litre(2),but the plasma potassium is 0.5 meq per litre lower(12). It is important to note that the total body potassium is lower in females and in older patients, but the serum potassium is not related to gender and age(12).This clinical range of normal serum potassium is narrow and very minimal deviation of serum potassium from this range (as small as less than 1.0 meq per litre) can lead to significant defects in the body which can even result in the death of the patient(13,14). Although this much deviation (of only 1.0 meq per litre) in concentration of serum potassium is small in absolute terms, the change in the intracellular to extracellular potassium ratio is by 25%(12). This is the reason why rapid evaluation of any deviation from the normal range of serum

potassium (hypokalemia or hyperkalemia) is needed and, whenever it is indicated, to treat the same is of critical importance.

GLOBAL EPIDEMIOLOGY

Hypokalemia is a common electrolyte abnormality encountered in hospitalized patients. Record linkage analysis of hypokalemia in patients who were hospitalized, done in Glasgow Royal Infirmary for a period of 3 years, showed the following results(15) :

a) At admission the number of patients having hypokalemia with a serum potassium of less than 3.5 meq per litre was 21%
b) Amongst these, patients who had clinically significant hypokalemia was 5.2 % with the value of serum potassium being less than 3.0 meq per litre.
c) There was significant association of hypokalemia with an increase in hospital mortality. Patients who died mostly had a serum potassium < 2 meq per litre (mortality 34%) and 2.0 to 2.4 meq per litre (mortality 26%)
d) A statistically significant gender difference was found with the female gender being more predisposed to the development of the same (a similar association had been reported previously from a study done in Denmark by Krakauer and Lauritzen in 1978). The reason as to why this kind of difference exists is not clear.
e) A strong and consistent relationship between hypokalemia and cancer as the main diagnosis at discharge was observed. Hematological malignancies were the most important cause for severe hypokalemia. On the other hand, tumors of the gastrointestinal tract seemed to cause hypokalemia of lesser degree of

severity. Relationship with other types of tumors was not statistically significant.

f) Most likely underlying cause (overall) was drugs (in about 38% of cases). Amongst the drugs, the most common one responsible for hypokalemia was found to be diuretics(62%) followed by steroids(9%) and then insulin(7%) and hydroxycobalamine(7%). Amongst patients on diuretics, the patients mostly had mild to moderate (2.5 to 3.4 meq per litre) hypokalemia both with thiazides and loop diuretics. The other mentioned drugs did not seem to correlate with the degree of hypokalemia. Intravenous fluid administration with insufficient potassium supplementation was also found to be responsible for hypokalemia.

Another study done in Jakarta, Indonesia in 2006 amongst patients with infectious diseases reported the following findings(16):

a) The age range was 14 to 70 years
b) Prevalence of hypokalemia among the hospitalised patients was 23% at admission and 37% during hospital stay. 5 % had serum potassium level less than 3 meq per litre.
c) Factors which seemed to be responsible for the development of hypokalemia were decreased intake of potassium in the diet and shift of potassium into the cells.
d) Most common associated infectious condition was found to be dengue.
e) The mean level of hypokalemia at admission was found to be 3.11 + SD 0.37 meq per litre and during hospitalisation was 3.13 + SD 0.25 meq per litre.

f) The ratio of hypokalemia in terms of severity , mild: moderate: severe , at admission was found to be 22:2:1 and that at discharge , moderate: severe, was 19:1

In a recent cohort study done in 2014 among patients who were admitted with hypokalemia in acute critical care setting in a University hospital located in Denmark(17) ,

a) Hypokalemia was found to occur in 16.8% amongst patients who were getting admitted for the first time, with plasma potassium level of <2.9 mmol/L occurring in 3.3% of patients. The former was notably lower than that which has been reported in previous studies- 24.9% and 20.4%.
b) The in-hospital mortality rate among patients with hypokalemia (serum potassium<3.0 mmol/L) was 7.9%(0-7 day mortality) and 9.4%(8-30 day mortality)
c) The prognostic factors for both the groups were found to be an increase in the age and Charlson co-morbidity index. There was no significant prognostic association found between prognosis and the continuing usage of diuretics or beta adrenergic agents.

Usually hypokalemia does not produce any symptoms and identified only on routine screening, but, severe hypokalemia can lead to serious problems like cardiac arrhythmias, paralysis, rhabdomyolysis, and diaphragmatic paresis. Many studies have looked into the causes and the symptoms of hypokalemia. However, the risk factors and prognosis of hypokalemia have mostly been studied in patients with

cardiovascular or chronic kidney disease(18–22). It was seen in these studies that even mild to moderate hypokalemia was associated with increase in morbidity and mortality upto 50%. It is not clear as to whether such an association exists in patients with other comorbidities.

Several electrocardiographic changes related to hypokalemia have been described in literature(23). The earliest change is a decrease in the amplitude of T-wave. As potassium level drops further, ST-segment depression and T-wave inversions as well as prolongation of PR interval and increase in the amplitude of P wave are seen. The U wave is best seen in the mid precordial leads (e.g., V2, V3). Prolongation of QU interval with an absent T wave (pseudo QT prolongation) may also be seen. Various arrhythmias can occur, mainly tachyarrhythmias and rarely, atrioventricular block.

The mainstay for the treatment for hypokalemia is replacement of potassium. However, care should be taken not to overcorrect. In fact, overcorrection is the most common reason for severe hyperkalemia in hospitalized patients(24). This problem is maximum with usage of intravenous potassium. Hence, the same should be avoided as much as possible. Routes by which potassium can be used are intravenous (mainly for severe hypokalemia) or oral (for mild to moderate hypoklaemia). Intravenous doses should not be given more than 20 meq per hour (0.75 gram per hour)(2). Usually, decrease in the serum potassium by 0.3 meq per litre implies a total deficit of 100 meq(2). Therefore, for a patient with serum potassium of 2.6 meq per litre , at least 300 meq of potassium is needed for correcting the deficit. However, in calculating the deficit, other factors also have to be considered which can independently affect the serum potassium like metabolic acidosis.

INDIAN EPIDEMIOLOGY

There are several case reports on the various clinical presentations of hypokalemia, including renal tubular acidosis, hyperthyroidism and Conn's syndrome as the etiological causes. However, no prospective observational study on hypokalemia has been done so far.

PATHOGENESIS

The normal regulation of potassium in the body is brought about by certain important hormones. Insulin and catecholamines (beta adrenergic) stimulate Na-K-ATPase located on the cell membrane(5). There is a feedback loop which exists in case of insulin whereby an increase in potassium leads to insulin secretion and decreased potassium inhibition of the same(25,26). Such a kind of mechanism does not exist in case of catecholamines (beta adrenergic). It has, however, been seen that the blocking of beta receptors leads to hyperkalemia and stimulation of the same leads to hypokalemia. This kind of effect is not dependent on the body stores of potassium.

Thyroid hormone also causes stimulation of the Na-K-ATPase(5). This may lead to hypokalemia that is sometimes seen in patients with hyperthyroidism.

The addition of alkali can lead to the movement of potassium into the cells(27,28). The response, however, is variable. This response is very slight in patients with chronic kidney disease stage V.

Aldosterone mainly acts on the kidneys and brings about the excretion of potassium(7). It is not clear whether it causes any shift of potassium into the cells. It,

just like insulin, also has a feedback loop by which an increase in potassium stimulates it's release and decrease in potassium inhibits it(8,9).

There are other hormonal as well as non hormonal factors that influence the excretion of potassium from the kidneys, but they do not seem to play a part in normal potassium homeostasis.

Table 1: Factors influencing the excretion of potassium in the kidneys

Increased Potassium Excretion	Decreased Potassium Excretion
Aldosterone	Absolute aldosterone deficiency or Resistance to aldosterone effects
High sodium delivery to the Collecting ducts(eg, diuretics)	Low sodium delivery to the collecting duct
High urine flow(eg, osmotic diuretics)	Low urine flow
High serum potassium levels	Low serum potassium levels
Delivery of negatively charged ions to the collecting duct(eg, bicarbonate)	Renal failure

The following are the pathogenic mechanisms which lead to hypokalemia:

1) **DECREASED INTAKE**

If the potassium in the diet is decreased to less than 1g per day (25 meq per day), there is a fall in the serum potassium level since there is no immediate reduction in potassium excretion through the kidneys in response to this kind of depletion(29,30).

It is rare to see this kind of hypokalemia for which the underlying cause is inadequate dietary intake alone(31). Even with starvation or near-starvation, there is depletion of potassium stores in the body, but along with this there is breakdown of tissues leading to release of potassium which helps to take care of the hypokalemia.

On ingesting low calorie diets containing a total calorie of 200 to 800 kilocalories per day, there can be hypokalemia. This is especially seen if patients do not take potassium supplementation or they have an underlying condition which is prone to the development of hypokalemia due to loss of potassium through the kidneys like primary aldosteronism. Such patients have normal baseline serum potassium (32–34). Example for such a kind of diet (mainly have the goal to decrease body weight) which have low carbohydrate and high protein is Atkin's diet. The exact mechanism as to why hypokalemia occurs on taking such kinds of diet is not understood fully. One mechanism that is thought of is the loss of potassium through its excretion in the kidneys. This was because it has been seen that in obese patients there is increased loss of potassium through the kidneys for the first two weeks on fasting or eating a diet low in carbohydrates(35). The reason for the loss of potassium could be due to production of ketone bodies as a consequence of intake of a diet poor in carbohydrate.

Clay ingestion (also known as geophagia) is a rare cause for hypokalemia. The earliest reported case was in 1964 by Mengel and associates(36). The possible mechanism postulated was the ability of some clay to bind and trap potassium in the lower gastrointestinal tract. They saw a similarity between their patient's clinical presentation and that which has been described more than 150 years back by Cragin

and Carpenter as cachexia Africana. Subsequently, there have been several case reports describing similar effect of hypokalemia on ingestion of clay(37,38).

2) INCREASED EXCRETION

Renal losses

In this, there is increased excretion of potassium through the kidneys. The mechanisms for the same are as follows:

i) *Increased delivery of sodium to the collecting duct(eg, with diuretics, osmotic diuresis, salt wasting nephropathies)*

Diuretics

One of the most common drugs causing hypokalemia is diuretics, mainly the thiazide and the loop diuretics. However, it must be remembered that any diuretic that has its action at a site which comes before the potassium secretion site can cause hypokalemia. This includes carbonic anhydrase inhibitors like acetazolamide along with thiazide and loop diuretics. Thiazides and loop diuretics act by chloride-associated sodium reabsorption, thiazides acting on the distal convulated tubule and the loop diuretics acting mainly on the loop of henle and also on the proximal and distal convulated tubules. This leads to increased sodium entry into the collecting tubules where the same gets reabsorbed forming a suitable electrochemical gradient for potassium secretion(9). Additionally, diuretics also cause secondary hyperaldosteronism. It is interesting to note that thiazides cause hypokalemia to a greater extent than do the loop diuretics despite the fact that they have a lesser

natriuretic effect. This may be secondary to decrease in the calcium excretion caused by thiazide whereas the loop diuretics cause the opposite effect(39). Therefore, in case of loop diuretics, the amount of the luminal calcium in the tubules is increased, which inhibits the ENaC channels in the principal cells. This in turn decreases the luminal negative potential difference leading to an increase in the excretion of potassium.

Some of the features seen in the usage of diuretics is as follows:

a) The dose and degree of hypokalemia are directly related to each other in case of thiazide diuretics(40,41). The severity is much more when sodium in the diet is increased. Hence, with lower doses, hypokalemia is less common. This is the reason why there is increased usage of thiazides in lower doses (12.5 to 25 mg per day of either chlorthalidone or hydrochlorthiazide) for treating patients with hypertension as , at the said doses, they are effective in controlling elevated blood pressures with much less effect on the electrolytes(42) . There were two large trials done to see the effect of chlorthalidone on hypertension(43,44). These trials showed that in such patients the occurance of hypokalemia which needed treatment was about 7 to 8 percentage. Also in stable patients (who have been on a fixed diuretic dose), the loss of potassium occurs in the first two weeks of starting treatment. Thereafter, there is formation of a new steady state. It is thus important to note that a patient, who has been stable with a serum potassium within the normal range for about three weeks after initiation of a diuretic, is not at a danger of developing a late onset hypokalemia (unless there is an increase in the dose of the diuretic or an increase in extrarenal losses or there is a decrease in the amount of potassium ingested in diet). Unless the

latter happen, there is no necessity of further follow up of serum potassium in such patients once a steady state has been established. Perchance a patient on diuretic therapy for hypertension develops hypokalemia, then an alternative drug needs to be started or there should be an addition of a potassium sparing diuretic to treat the hypokalemia or supplementation of potassium needs to be done.

b) Combining furosemide or bumetanide with metolazone almost always leads to a decrease in the serum potassium concentration (moderate to severe) even if potassium is supplemented(45).
c) Hypokalemia due to diuretics is often accompanied with metabolic alkalosis. Exception to this is acetazolamide which causes metabolic acidosis(45).

Other drugs

Amongst other drugs which can cause hypokalemia through the mechanism of increasing renal potassium excretion are penicillin and its synthetic derivatives, aminoglycoside antibiotics, cisplatin, foscarnet. Penicillin and its derivatives act by causing an increased sodium delivery to the distal convulated tubule. The remaining drugs cause magnesium depletion and hence, cause hypokalemia(46,47).
Amphotericin B is another drug which causes hypokalemia by two mechanisms: (i) Increased potassium excretion through the kidneys by blocking the secretion of hydrogen ions by the kidney. (ii) Causing depletion of magnesium. Laxatives, if given in large doses, can cause loss of potassium in faeces. This can cause hypokalemia. Similar effects are seen with repeated enemas.

Osmotic diuresis

Patients with uncontrolled diabetes mellitus have an increase in the glucose load to the kidneys and hence there is osmotic diuresis due to the same. This leads to an increased sodium delivery to the distal tubule which supports potassium excretion. If the increased glucose excretion through the kidneys (renal glycosuria) continues for a long time, it can lead to a significant depletion of potassium stores in the body(48). This kind of hypokalemia is mostly mild or absent, the reason being that both the increase in osmolality and the decreased insulin levels prevent shift of potassium from the extracellular compartment to the intracellular compartment. In such a situation , when insulin is administered , there is accelerated unmasking of the underlying hypokalemia, leading unto the development of severe hypokalemia, especially in patients who have diabetic ketoacidosis, unless effective measures are taken to replace the body stores of potassium simultaneously.

ii) *Excess of mineralocorticoids (eg, primary or secondary hyperaldosteronism)*

Mineralocorticoids can be excess in the true sense or there may be a state of apparent mineralocorticoid excess.

Table 2. Mineralocorticoid excess- Causes

Primary hyperaldosteronism (Aldosterone producing adenomas)
Primary or unilateral adrenal hyperplasia
Idiopathic hyperaldosteronism due to

A) Bilateral adrenal hyperplasia B) Adrenal carcinoma
Familial hyperaldosteronism (FH-I,FH-II,Congenital adrenal hyperplasias)
Secondary hyperaldosteronism (malignant hypertension, renal secreting tumors, hypovolemia)
Cushing's Syndrome
Bartter's syndrome
Gitelman's syndrome

Table 3.Apparant mineralocorticoid excess- Causes

11Beta-Dehydrogenase-2- Genetic deficiency (syndrome of apparent mineralocorticoid excess)
Inhibition of 11Beta-Dehydrogenase-2 by a) glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone b) licorice c) food products d) drugs
Liddle's syndrome

Aldosterone acts on the ENaC channels located on the principal cells of the collecting duct by a number of synergistic mechanisms and causes its activation(7,39). This

causes an increase in the driving force for potassium excretion leading on to hypokalemia.

Primary and Secondary hyperaldosteronism:

Increases in aldosterone level in the circulation could either be primary or secondary. In seconday hyperaldosteronism, there in an increase in the level of circulating renin which in turn leads to an increase in the level of angiotensin II(AT-II) and hence aldosterone. The most common cause of secondary hyperaldosteronism is renal artery stenosis(39). Most of the patients with primary hyperaldosteronism have a normal serum potassium level(49). This occurs because of the fact that the potassium excreting action of aldosterone is countered by the potassium retaining action of hypokalemia. Usually, in these patients, the potassium level falls only if there is an addition of another inciting agent like a diuretic.

The causes of primary aldosteronism can be genetic or acquired.

Genetic

In congenital adrenal hyperplasia, there are problems in either steroid 11-hydroxylase or steroid 17-hydroxylase. The hypertension and hypokalemia which occur in such patients are due to increase in the blood level of 11- deoxycorticosterone.

Isolated primary hyperaldosteronism occurs in two major forms:

a) Familial hyperaldosteronism type I(also known as glucocorticoid remediable hyperaldosteronism).

b) Familial hyperaldosteronism type II where aldosterone production cannot be suppressed by glucocorticoid administration.

FH-I is caused by a chimeric gene duplication between the homologous 11-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) genes.

Aquired

Acquired causes are:

Aldosterone-producing adenomas

Primary or unilateral adrenal hyperplasia

Idiopathic hyperaldosteronism due to bilateral adrenal hyperplasia

Adrenal carcinoma

Amongst these, aldosterone producing adenomas and idiopathic hyperaldosteronism are the most common causes (account for about 60% and 40% of diagnosed cases of hyperaldosteronism respectively)(39)

Cortisol (a glucocorticoid) has affinity for the mineralocorticoid receptor(MLR) equal to that of aldosterone.. Hence, it has additional mineralocorticoid like activity. This effect, however, does not occur in the cells of distal nephron which are aldosterone sensitive. Such a kind of sparing of the distal cells from this action of cortisol is due to the enzyme 11-hydroxysteroid dehydrogenase-2, which changes cortisol to cortisone(50,51). Genetic mutations in the 11HSD-2 gene therefore leads to cortisol-dependent activation of MLR and hence the syndrome of apparent mineralocorticoid

excess. In this syndrome, there is hypertension, hypokalemia, hypercalciuria and metabolic alkalosis(52). The plasma renin activity and aldosterone are suppressed. There can be various substances which lead to similar syndrome by blocking of 11 Hydroxysteroid dehydrogenase-2 enzyme(53). These substances include glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone. Glycyrrhizinic acid is a sweetner (natural) found in licorice root.

Hypokalemia also occurs secondary to increased glucocorticoids in the circulation. The incidence of hypokalemia in Cushing's syndrome due to increase in pituitary ACTH is 9 %, but in those where the underlying cause is an ectopic secretion of ACTH, it is 50%(54). There are indirect evidences which show that there is decreased in the action of 11- Hydroxysteroid dehydrogenase-2 in patients who have ectopic production of ACTH.

In Primary hyperaldosteronism and Cushing's syndrome, there is chloride resistant metabolic alkalosis(55).

Heriditary hypokalemic alkalosis can be caused by the loss of the transport functions of the loop of henle(thick ascending limb) as well as the distal convulated tubule(56). Examples for these are Bartter's and Gitelman's syndrome.In case of Bartter's syndrome, thick ascending limb of the loop of henle is affected(five genes are involved) whereas in Gitelman's syndrome, the distal convulated tubule is affected(loss of function mutations in the thiazide-sensitive Na+,Cl- cotransporter located in distal convulated tubule). There is occurance of metabolic alkalosis and hypokalemia without hypertension in both theses genetic syndromes. Bartter has an

effect similar to the chronic usage of loop diuretics; Gitelman has an effect similar to the chronic usage of thiazide diuretics.

In Liddle's syndrome [genetic activation of epithelial Na+ channels (ENaC)], there may be hypokalemia due to an apparent minerolocorticoid excess(57). This is an autosomal dominant disorder in which there is gain of function mutation in the sodium channels. In this syndrome there is metabolic alkalosis and hypokalemia along with hypertension which is similar to 11 Beta-hydroxysteroid dehydrogenase deficiency.

Drugs with mineralocorticoid or glucocorticoid effects

Oral mineralocorticoid, fludrocortisone, causes the excretion of potassium through the kidneys. Therefore, if this drug is used inappropriately, then it can lead to loss of potassium from the body and clinical manifestations of hypokalemia. On the other hand, glucocorticoids do not directly influence the secretion of potassium in the kidneys , but they do increase the excretion of potassium through mechanisms which are not specific(28). They effect the glomerular filtration rate and the amount of sodium moving to the distal convulated tubule. However, long term usage of these drugs produce only a minimal decrease in the serum potassium concentration. There are other drugs like Gossypol, carbenoxolone, and licorice which inhibit the activity of 11 Beta-hydroxysteroid dehydrogenase, leading to hypokalemia(58,59).

iii) Increased urine flow (e.g., osmotic diuretics)

Osmotic diuretics (like mannitol) mainly cause hypokalemia by increasing the distal tubular flow(60).

iv) Metabolic acidosis

One of the cardinal manifestations of type I or classic distal renal tubular acidosis is hypokalemia. The amount of hypokalemia in this disorder mainly reflects intake of sodium and potassium in the diet and the concentration of aldosterone in the blood. It does not directly correlate with the amount of acidosis. If a patient with distal renal tubular acidosis is left untreated, then it can lead unto severe hypokalemia which can be life threatening. Treatment with sodium bicarbonate corrects the hypokalemia(61), but these patients usually need to be on supplementary potassium for long period of time(62). In contrast, in patients with proximal or Type II renal tubular acidosis, hypokalemia occurs only occasionally in patients who have not been treated. It often develops when these patients have been given sodium bicarbonate(63).

v) Magnesium depletion and Hypokalemia

Fall in magnesium levels in the blood can lead unto hypokalemia and renal potassium wasting(47). The decrease in the level of magnesium in the blood can be due to either decreased dietary intake or by abnormal losses. At times of magnesium depletion, the intracellular level of potassium gets reduced due to inactivity of the Na+-K+ATPase pump. However, the mechanism by which the decrease in magnesium level leads to wasting of potassium through the kidneys is unclear. Many a times, the deficiency of magnesium and potassium may be coexisting in a patient. The cause may be drugs or diseases in which there is loss of both these electrolytes. This makes it complex and difficult to know whether the decrease in the serum potassium is an independent problem or is due to decrease in magnesium(47).

vi) Others

Some haematological malignancies can cause severe and refractory hypokalemia, namely, acute myelogenous, monomyeloblastic and lymphoblastic leukemias(64,65). In these disorders, there is increased loss of potassium through the kidneys. The reason as to why this kind of loss occurs is not known. It is also seen that once there is remission of these disorders, the hypokalemia also settles.

Salt wasting nephropathies: Diseases of the kidney where there is a defect in the function of the proximal convulated tubule or the loop of henle or the distal convulated tubule(affection of distal reabsorption of sodium) can many a times lead to hypokalemia. The underlying mechanism is like that which is caused by the effect of diuretics. Some examples of disorders producing this kind of effect are Bartter syndrome, Gitelman syndrome, tubulointerstial diseases(like reflux nephropathy, interstitial nephritis in Sjogren's). Others are hypercalcemia, injury to the tubules by medications like cisplatin as well as that by lysozyme in leukemic patients as described above(17,66,67).

Gastrointestinal losses

Gastrointestinal losses(eg, diarrhoea, vomiting, nasogastric suctioning) are common causes of hypokalemia

Upper Gastrointestinal losses:

The amount of potassium contained in the gastric fluid is 5 to 10 meq per litre. Therefore, the decrease in potassium that occurs due to these causes is mainly due to increased excretion from the kidney(68). Vomiting and nasogastric drainage cause metabolic alkalosis (due to selective chloride depletion) and increase in the level of bicarbonate in the blood. These in turn cause an increase in the bicarbonate that is filtered more than that is reabsorbed. Therefore, an increased amount of bicarbonate along with water is carried to the distal tubule. Along with this, vomiting also causes a decrease in the plasma volume which leads to an increase in the plasma renin activity and hence, an increased aldosterone secretion thereby causing an increased amount of potassium to be excreted from the kidney. In order to check for the presence of decrease in plasma volume, the urine chloride value is checked which is low. This is the chloride sensitive form of metabolic alkalosis. In such cases, repletion of chloride through exogenous means helps in the correction of the metabolic alkalosis and therefore allows for the restoring of the body stores of potassium. However, the dietary intake of potassium should be adequate in such situations.

This kind of loss of potassium through the kidneys that is seen in patients who have loss of gastric fluid is maximally seen in the first few days. After this, the capacity for reabsorption of bicarbonate is increased which leads to a significant decrease in the amount of sodium, bicarbonate and potassium lost in urine(68). There a decrease in the urinary pH from more than 7 to less than 6.

*Lower Gastrointestinal Losses***:**

The amount of potassium contained in the lower gastrointestinal tract fluid is comparatively higher than that contained in the upper gastrointestinal fluid (as high as 20 to 50 meq per litre). In these kind of losses, there is wasting of bicarbonate and metabolic alkalosis with increased levels of chloride(hyperchloremic metabolic alkalosis). It is to note here that there may also be hypokalemia which is caused due to factitious diarrhoea or the abuse of laxatives. These patients develop metabolic alkalosis through a mechanism which is not known.

At an average, the amount of potassium that is taken in diet is about 80 meq per day. If there is hypokalemia, then the amount of fall in the excretion of potassium through urine should be 15 to 25 meq per day(68). The normal amount of potassium that gets excreted in stool is about 10 meq per day. This amount must go beyond 55 to 65 meq per day for the serum potassium to fall and for the patient to become hypokalemic. Interestingly, many patients who have diarrhoea and become hypokalemic have a level of potassium in the stool not beyond but below this level. This implies that other factors also have a part to play in the decrease of the serum potassium like a decrease in the oral intake and a decrease in the plasma volume leading to increased activity of aldosterone(69). Whenever there is diarrhoea, the volume of faeces increases which in turn leads to significant amount of potassium depletion and hence hypokalemia.

Hypokalemia that occurs due to the loss from the lower gastrointestinal tract usually occur when the same occur over a very long period of time. Examples for prolonged diarrhoea are that occurring with villous adenoma, a VIPoma(Vasoactive Intestinal

peptide secreting tumor), infectious diarrhoea which are persistent (69–71). Hypokalemia due to lower gastrointestinal losses is especially important in tropical infective conditions like malaria and leptospirosis.

There are some other causes in which there is loss of potassium through the lower gastrointestinal tract. These are:

a) Colonoscopy preparation: While preparing the bowel for colonoscopy with agents like sodium phosphate, polyethylene-glycol based preparations(especially in elderly individuals) (72,73)
b) Ogilvie's syndrome: Otherwise known as colonic pseudoobstruction has secretory diarrhoea as its clinical manifestation. In this there is an increased potassium in the faeces due to stimulation of the secretion of potassium in the colon.

Sweat

Excretory losses of potassium can also occur through sweating. A study conducted in 2001 showed that among soccer team players in a high school (while they were actively training), the mean amount of iodine, sodium, potassium and calcium lost in sweat were 52 microgram,1.896 microgram, 248 mg, and 20 mg respectively(74). Loss of potassium in the sweat daily is normally very minimal and insignificant. The concentration of potassium in sweat per day is about 5 to 10 meq per litre only, but , in people who are working in a hot environment or climatic conditions the production of sweat goes more than or equal to 10 litres per day. This can lead to the loss in

potassium stores if replacement is not done. A lot of potassium loss through sweat can also be a manifestation of cystic fibrosis(75). One more factor which may add to the potassium loss is the exercise induced stimulation of the release of aldosterone leading unto increased loss of potassium through excretion in the kidneys(74,76).

3) EXTRACELLULAR OR INTRACELLULAR SHIFT

Often this mechanism occurs along with increased excretion of potassium through the kidneys, which leads to an incremented effect on the loss of potassium. Many a times, the intracellular shifts are episodic. Frequently, they are self-limited (e.g., acute insulin treatment for hyperglycemia).Whatever be the cause for hypokalemia, it produces similar signs and symptoms. Since potassium is an intracellular cation(3) and a huge number of factors can influence the actual serum potassium concentration, there can be significant loss of potassium without exhibiting frank hypokalemia. This can be seen in patients with diabetic ketoacidosis where there is significant potassium deficit, but the serum potassium in such patients is rarely low and many a times is frankly elevated(77).

On the other hand, hypokalemia may not always be a representation of a true deficit in the body's total potassium stores. For example, on administering insulin acutely, it can push potassium transiently into the cells, leading unto hypokalemia for a short while but this does not indicate potassium depletion(45).

TRANSCELLULAR SHIFTS-DRUG INDUCED

Beta2-Sympathomimetic Drugs

Examples of Beta2 adrenergic agonists are:

Epinephrine

Decongesants like Pseudoephedrine and phenylpropanolamine

Bronchodilaters like albuterol, terbutaline, pirbuterol, isoetharine, fenoterol, ephedrine, isoproterenol, metaproterenol

Tocolytic agents like ritodrine, nylidrin

It has been seen that the reduction in seum potassium by a standard dose of albuterol (nebulized) is about 0.2 to 0.4 meq per liter. On repeating the dose after 1 hour, the reduction is by about 1 meq per liter(78,79). The effect lasts for about four hours. Similarly, ritodrine and terbutaline, on being administered intravenously for 4 to 6 hours, can lead to a decrease in serum potassium to as much as 2.5 mmol per liter(80). Pseudoephredine overdose can also lead to severe hypokalemia(81).

There also have been case reports which have described hypokalemia in patients due to exposure to heroin or meat products that have been mixed with sympathomimmetic(beta agonist) agents like clenbuterol(82)

Whatever be the underlying reason for increased beta adrenergic stimulation, the amount of hypokalemia will be more in those patients who already have decreased serum potassium due to causes like diuretics(83).

When is it that the hypokalemia induced by the administration of beta stimulators likely to produce arrhythmias? This may be seen in the following instances:

- On administering along with a diuretic simultaneously in hypertensive individuals(84).
- In pregnant women who have preterm labour(85)

Theophylline and other Xanthines

There are two mechanisms by which theophylline and other xanthines and caffeine act(86). Firstly, they cause a stimulation of the release of sympathetic amines. Secondly, they inhibit cellular phosphodiesterase leading to an increase in the activity of Na-K-ATPase activity. Acute toxicity with theophylline leads to severe hypokalemia(86,87). Caffeine content in a few drops of coffee brings down the serum potassium by about 0.4 meq per liter(88).

Other drugs

CALCIUM CHANNEL BLOKERS

Calcium channel blockers, at usual doses, do not influence the serum potassium concentration. If, however, overdose occurs with verapamil, it leads to severe hypokalemia by increasing the entry of potassium into the cells(89).

INSULIN

Insulin causes potassium to move from the extracellular space to intracellular space. It always causes a transient decrease in the serum potassium concentration. Therefore, the decrease in serum potassium caused by insulin is not a major clinical problem

except during times of overdose(86) or while diabetic ketoacidosis is being managed. This hormone brings about the movement of potassium into the skeletal muscle cells and hepatocytes. Its action is mainly on the Na-K-ATPase pump(90), whereby its activity is increased leading to the entry of potassium into the cells. This kind of effect due to insulin is most prominently seen on administration of insulin exogenously(for example, in patients with diabetic ketoacidosis or severe hyperosmolar non ketotic hyperglycemia- these patients are many a times normokalemic when they initially come to the hospital even though there would have been depletion of potassium in them)(77). Insulin overdose can rarely cause hypokalemia(86).

On intake of an increased amount of carbohydrate in the diet, there is release of endogenous insulin which can lead on to hypokalemia(for example, as can be seen in refeeding syndrome(91) and after giving intravenous potassium in an intravenous fluid containing dextrose solution in water)

CHLOROQUINE INTOXICATION

One common feature in patients with acute poisoning/overdose with chloroquine is that the serum potassium level falls less than 2 meq per litre(86). The mechanism of this kind of effect of chloroquine is possibly due to the movement of potassium into the cells and the same can be amplified if epinephrine is used to treat the toxicity. Also it inhibits the movement of potassium out of the cells.

CESIUM INTOXICATION

Most of the times, intoxication with caesium occurs as a result of the usage of cesium chloride an an alternative treatment for cancer. This can cause hypokalemia(92). The

reason as to why this occurs is not clear, but could be due to the blocking of the potassium channels located in the cell membrane by cesium(93).

ANTIPSYCHOTIC DRUGS

Certain antipsychotic drugs like resperidone and quetiapine can cause hypokalemia. But this is a rare adverse effect(94,95).

TRANSCELLULAR SHIFTS- NONDRUG RELATED

Elevated extraxellular pH

There can be two situations in which there is elevated pH, metabolic alkalosis and repiratory alkalosis. Such conditions can lead to the entry of potassium from the extracellular compartment to the intracellular compartment. The reason as to why this kind of movement occurs is that whenever there is an alkalosis, there is movement of hydrogen ions out of the cells. Hence, to maintain a state of electrical neutrality, it is necessary for some potassium ions (as well as sodium ions) into the cell. The fall in serum potassium for every 0.1 unit rise in pH is 0.4 meq per litre(96).

It must however be remembered that though alkalemia causes hypokalemia by transcellular shift, it is common to find metabolic alkalosis in hypokalemia. The reason for this is that the prime causes of hypokalemia(for example diuretics, vomiting, hyperaldosteronism) also cause a movement of hydrogen ions out of the cell.

Decreased serum potassium also brings about the reabsorption of bicarbonate and hence, hypokalemia is important as a cofactor in maintaining metabolic alkalosis, thus causing an impairment of the rectification of the alkalemia by the renal clearance of the increased bicarbonate.

Hyperthyroidism related

Moderate to severe hypokalemia (serum potassium< 3.0 meq per liter) can rarely occur in patients with hyperthyroidism(97). The manifestation of the same may be muscle weakness and paralysis. This can be of sudden onset and severe. People of Asian origin have an increased chance of developing this kind of symptom. It occurs in about 2 to 8 percent of Asian patients with hyperthyroidism. Despite the fact that there is increased occurance of thyrotoxicosis in women, men, especially those of Asian origin, are more likely to manifest this complication. The manifestations of an attack of thyrotoxic periodic paralysis resemble those of primary Hypokalemic periodic paralysis. These episodes settle with treatment of the underlying hyperthyroidism. The muscle weakness can be episodic and acute. The clinical features of hyperthyroidism usually occurs along with these episodes, though may be subtle. These episodes have a rapid improvement on replacement of potassium.

Hypokalemic periodic paralyses- Familial

This is a rare autosomal dominant disease with incomplete penetrance. This disorder is caused due to mutations in one of the two genes(98,99):

a) voltage-sensitive skeletal muscle calcium channel gene, CALCL1A3 – Hypokalemic Periodic Paralysis type 1

b) voltage sensitive sodium channel gene SCN4A- Hypokalemic Periodic Paralysis type 2

Hypokalemic periodic paralysis Type 1 accounts for 90 % of cases and Hypokalemic periodic paralysis type 2 is responsible for 10% of cases(39). These mutations lead to the generation of an aberrant gating pore current which makes the muscle cell to depolararize whenever there is hypokalemia.The usual age of onset is adolescence. Gender difference is seen in terms of men being more often affected than women as there is decreased penetrance in the female gender. Episodic sudden attacks of muscle weakness occur with a low serum potassium concentration, many a times less than 2.5 meq per liter. Such episodic attacks with the age of onset being more than 25 years almost never has periodic paralysis as the underlying aetiology the exception being that of thyrotoxic periodic paralysis. Various factors are there which can trigger an attack, including high intake of carbohydrates or sodium and physical exertion. These inciting events are accompanied with an increased release of epinephrine or insulin (both of which are responsible for causing transcellular shift of potassium into the cell and hypokalemia)(100). The clinical finding that may be seen in these patients is that there is weakness of the proximal group of limb muscles much more than the distal muscles. The muscles which are less likely to be involved are the ocular and bulbar muscles. The muscles that assist in respiration are usually not involved but, perchance, they do get involved, the patient may die. These attacks usually get better within twenty four hours. During times of attack, there may be development of cardiac arrhythmias that can be life threatening. One late complication that may happen in these patients is the development of severe, lower limb weakness involving the

proximal group of muscles which disables the patient. The underlying mechanism for hypokalemia is shift of potassium from the extracellular to the intracellular space. The finding of a low value of serum potassium during attacks and with the exclusion of the other causes helps to establish the diagnosis of hypokalemic periodic paralysis. During the interval in between attacks, if a muscle biopsy is taken, it shows single or multiple vacuoles which appear at the centre or tubular aggregates. There are provocative tests which are available to establish the diagnosis with the usage of glucose and insulin. However, these tests are mostly not required. On the other hand, they can be harmful. If an electromyography is done during an attack, it shows decreased amplitude. In severely weak muscles, the same may show and electrical silence. During the interval periods, the electromyography and nerve conduction velocities are normal, except the presence of myopathic motor unit action potential in candidates who have fixed weakness. These patients have a low urine potassium excretion which is a distinguishing feature from renal causes of hypokalemic paralysis(101). Replacement of potassium is often life saving and is indicated for the treatment of attacks. The monitoring of the muscle power and electrocardiogram should be done. Usually the administration of potassium orally is enough, intravenous therapy is rarely required (for e.g., if the patient has any problem with swallowing or if the patient has vomiting). Syrup Potassium chloride may be given orally at a dose of 0.2 to 0.4 meq per kilogram every half an hour. If intravenous potassium replacement is done, then the preferred vehicle for the same is mannitol.

The long term aim of treatment is to prevent attacks. This is important as it may reduce the occurance of fixed weakness which occurs as a delayed complication in

such patients(102). Various prophylactic measures have been tried to prevent recurrences. The success rates have been variable. These methods include administration of spironolactone, triamterene, and acetazolamide(103). It has been seen that the prophylactic usage of acetazolamide at a dose of 125 to 1000 mg per day in divided doses helps to decrease or may even stop the attacks in hypokalemic periodic paralysis type 1. However, the administration of acetazolamide may lead to precipitation of an attack in hypokalemic periodic paralysis type 2.A paradoxical effect that is seen is further decrease in the serum potassium level. However, this is balanced by the beneficial effect of metabolic acidosis. Perchance the attacks persist despite acetazolamide, then oral supplementation with potassium chloride should be initiated along with acetazolamide therapy. There are some patients who may need treatment with triamterine or spironalactone. The doses of both these drugs are same, that is, 25 to 100 mg per day .

Delirium tremens

In delirium tremens, there is a sudden decrease in the serum potassium concentration by about 1.0 meq per liter(104). The decrease in serum potassium is presumed to be due to Beta2 adrenergic stimulation leading to movement of potassium from the extracellular space to the intracellular space.

Barium intoxication

Barium intoxication, either due to intentional or accidental ingestion(105), inhibits the shift of potassium from inside the cells to the extracellular space(106). In severe cases, there can be weakness and paralysis of muscles and rhabdomyolysis. Vomiting and

diarrhoea also occur which have an augmenting effect on the hypokalemia. In this poisoning, administration of intravenous potassium should be done as soon as possible(106). Another effective therapy is hemodialysis(107).

Vitamin B12 supplementation and blood transfusion

Treatment with Vitamin B12, for example, for severe pernicious anemia can lead to hypokalemia, the mechanism being increased uptake of potassium be the newly formed cells(108). Blood transfusion with washed red cells (previously frozen) can lead to hypokalemia due to the same mechanism(109).

Granulocyte macrophage colony stimulating factor

Literature also describes the development of hypokalemia in patients receiving granulocyte- macrophage colony stimulating factor(110). The underlying mechanism is again the shift of potassium from the extracellular compartment to the intracellular compartment. There is increased uptake of potassium by the hematopoietic cells.

Total Parenteral Nutrition

The administration of total parenteral nutrition leads to the development of various forms of electrolyte disturbances. Literature describes the occurance of hypokalemia to as much as 3 to 12% of surgical patients who were treated with total parenteral nutrition(111).

Hypothermia

Hypothermia can be either a presenting problem or it can be induced(as part of therapeutic hypothermia post cardiac arrest). Whatever be the underlying reason for

hypothermia, it can lead to a decrease in the circulating level of potassium(112). The mechanism for the same is transcellular shift of potassium from the extracellular compartment to the intracellular compartment rather than a loss. It is of importance that once should anticipate this electrolyte abnormality when a patient is hypothermic and prompt initiation of treatment for the same is indicated else it may progress unto severe hypokalemia and its consequences.

Pseudohypokalemia

Pseudohypokalemia or factitious hypokalemia is a term which is used to describe low biochemical values of serum potassium when the actual serum potassium in a patient is normal. This kind of effect is mainly seen in patients who have a high whole blood cell count (>100000 per microlitre) when the blood samples have been kept in room temperature for some time(113). Such a scenario is encountered in patients with acute leukemia. This kind of effect happens due to the movement of potassium into the leukemic cells. Factitious hypokalemia should not, however, be confused with true hypokalemia which occurs in patients with acute myeloid leukemia(especially the one with monocytic differentiation)(64). In the latter, the reason for hypokalemia is increased renal excretion of lysozymes which increases the excretion of potassium from the tubules.

JUSTIFICATION

This study is being done in order to check the occurance of the causes of hypokalemia in an Indian hospital setting. Hypokalemia can be detrimental as it can lead to cardiac arrhythmias and death. It is not only important for it to be detected and treated, but identification of the underlying cause is also equally necessary as catching that may provide long term solution to prevent recurrences of the former. How this electrolyte abnormality presents or the factors affecting it in an Indian setting is not known. Therefore, this study is being done to determine the same. It is also being done in order to see if there is any relationship between the dose and duration of treatment of hypokalemia and its severity

METHODS

The study proposal was approved by the Institutional Review Board on 15/01/2015.

STUDY DESIGN

The study was conducted in a tertiary care hospital, Christian Medical College and Hospital, Vellore, Tamil Nadu, South India, which is a 2062 bedded hospital. It was a prospective observational study with the aims and objectives as stated above. The patients were recruited from the medical wards being managed by the internal medical units in the institution. There are five such units who admit patients in four different wards. Prior to starting the study a retrospective pilot study was done in order to determine the sample size. In this retrospective study the proportion of patients admitted to the medical wards who had hypokalemia on the first day of admission

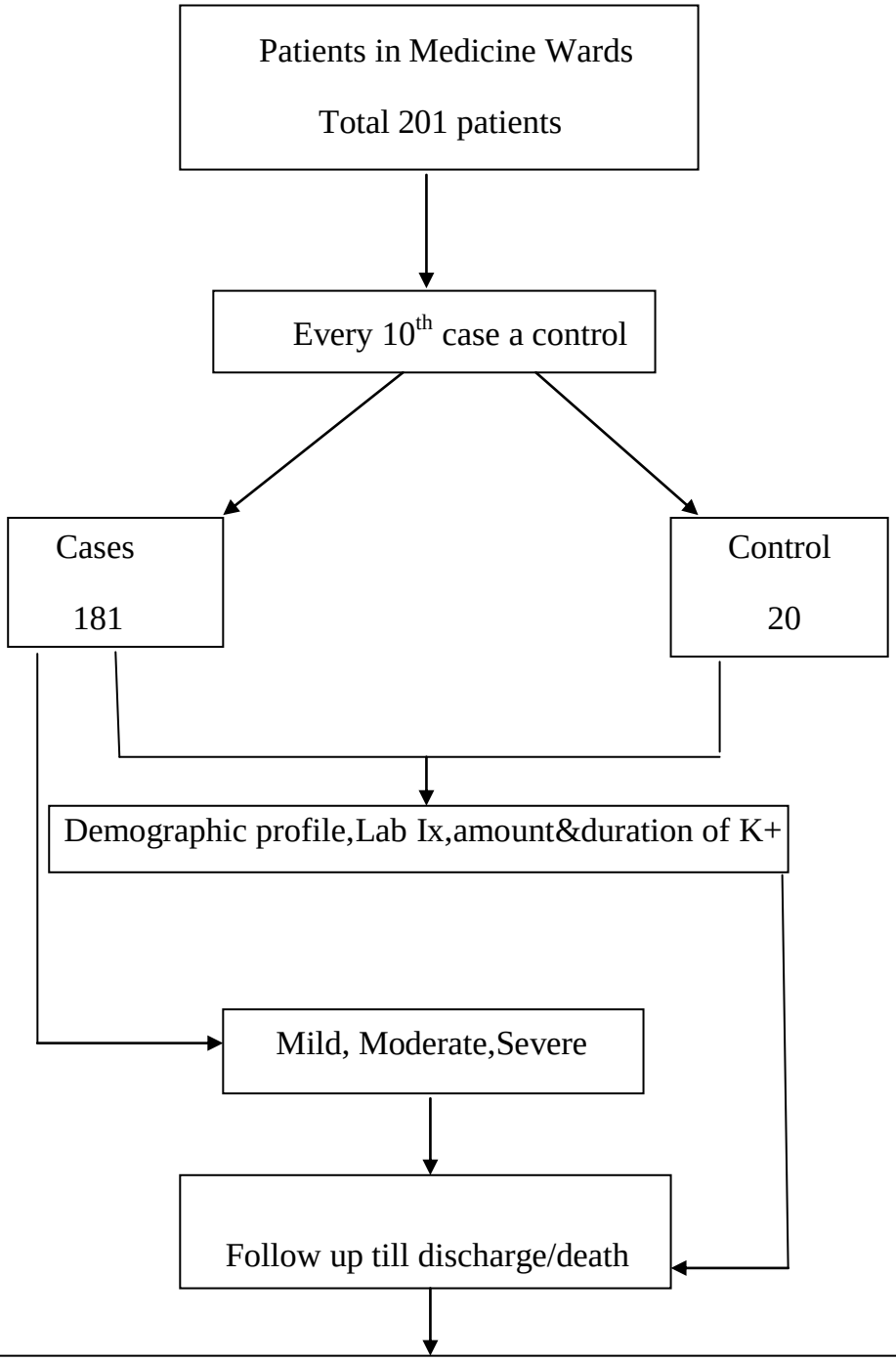
over a period of one year from April 2013 to March 2014 was calculated and a sample size of 200 was obtained.

The recruitment of patients began from March 1st 2015. The definition of hypokalemia based on literature and standard reference values was taken as a serum potassium of less than 3.5 meq per litre. Every consecutive patient with hypokalemia on day 1 of admisssion was recruited into the study. The controls were selected as every tenth consecutive patient who had serum potassium of more than or equal to 3.5 meq per litre. Consecutive recruitment was done based on the time of admission to the medical ward after taking a written informed consent. The same was determined by means of checking the inpatient chart of the patient which had the time of admission printed on it. The total number of cases was 181 and the total number of controls was 20. Post recruitment the data for each of the patient as well as control was collected. The data consisted of demographic profile, comorbidities, usage of any inciting agents in the past 3 months, the symptoms and signs that the patient had, electrocardiographic changes if the same had been taken and relevant laboratory investigations along with the final outcome in terms of discharge or death, the final primary diagnosis and the possible underlying cause. The demographic profile comprised the name of the patient, gender, the hospital number of the patient, the date of admission, the date of discharge, the occupation of the patient, the medicine unit admitting the patient,the state or the country (if the patient is from a country other than India) to which the patient belongs to, his address and communication number. Among the comorbidities, the data was collected for diabetes mellitus, hypertension, smoking, alcohol, ischemic heart disease, cerebrovascular accident, heart failure, peripheral vascular disease,

chronic obstructive pulmonary disease, chronic kidney disease , liver disease, dementia, lymphoma and any other comorbidity. The number of years of having the comorbidity was also noted. Data for the inciting agents used in the last three months prior to admission were mainly for loop diuretics or thiazide diuretics(if the patient was on these, the specific name was also required to be mentioned), usage of steroids in any form, inhaled beta-2 agonists, amphotericin B/azoles or echinocandins specifying the name, cytotoxic agents like cisplatin, hydrxycobalamine, theophylline/aminophylline or caffeine, digoxin, overdoses of quetiapine or verapamil. The recruitment was done till May 31st 2015 when the sample size was reached.

After recruitment, all the patients were followed up till discharge or death. The data that were collected during the time of follow up were the final outcome in terms of either discharge or death, the amount of potassium(oral, intravenous and both) used for correction of potassium in grams and the duration to achieve a normal serum potassium value of 3.5 to 4.5 meq per litre. For oral correction each 15 ml of syrup potassium chloride contains 1.5 grams of potassium. Based on this further calculation of the oral dose in grams was done. The data for both oral and intravenous corrections was obtained from the treatment charts of the patient during the time of hospital stay. After obtaining the above information, the data was analysed Thereafter results were obtained and conclusions drawn from the same.

Flow of patients



a) Proportion of patients with hypokalemia at admission and it's causes
b) Association of hypokalemia with mortality in comparision to eukalemic controls
c) Any observation in relationship of hypokalemia with comorbidities
d) Correlation of ECG changes with severity of hypokalemia
e) Dose and duration of potassium required for correction in each severity class

PATIENT POPULATION:

The patient population consisted of patients admitted in the medical wards with an admission potassium value of less than 3.5 meq per litre who fit into the inclusion criteria and gave a written informed consent. The consent was taken in a language that the patient was able to understand.

INCLUSION CRITERIA:

The following were the criteria for inclusion into the study:

(1) All patients admitted in the medical wards with hypokalemia at admission defined as a serum potassium of less than 3.5 meq/L

(2) Age more than or equal to 18 years

EXCLUSION CRITERIA:

There was only one exclusion criteria:

(1) Age less than 18 years

DEFINITIONS:

Mild hypokalemia: Serum potassium 3.0 to 3.49 meq per litre

Moderate hypokalemia: Serum potassium 2.50 to 2.99 meq per litre

Severe hypokalemia: Serum potassium less than or equal to 2.49 meq per litre

Normal potassium range: Serum potassium 3.50 to 4.50 meq per litre

INTERVENTION:

Since this is an observational study, no intervention was done.

CASES:

Any patient with serum potassium level of less than 3.5 meq per litre (excluding the value of 3.5 meq per litre) at day 1 of hospital admission

CONTROL:

The control group comprised patients who had a serum potassium value of more than or equal to 3.5 meq per litre. Every tenth consecutive patient admitted to the medical wards was taken as a control. There were 20 such controls.

OUTCOME:

The outcomes that were being studied were the following:

1. To find the proportion of patients of hypokalemia and its causes in adult medical wards.

2. The dose and duration of potassium(intravenous or oral or both) required for correction
3. Correlation of hypokalemia with mortality
4. Association of hypokalemia with other comorbidities
5. Association of ECG changes with severity of hypokalemia

THE INTERVIEW AND CONSENT:

All patients and controls who fulfilled the eligibility criteria were approached and were initially explained verbally about the study and that we wished to get their consent for the same. They were then given a written information sheet in a language which they could understand and were asked to read the same. If they had any doubts, the same was clarified. Thereafter, if they agreed to be included in the study, they were asked to sign a written consent in a language which they could understand.

THE DATA:

The data for demographic profile, comorbidities, use of inciting agents, symptoms and signs, were taken from the history sheet. The relevant laboratory data was taken from the patient's laboratory record. The amount and duration of potassium required for correction was calculated from the patient's treatment record. Data for the final outcome and final primary diagnosis was obtained from the discharge or the death summary of the patient. The possible underlying cause was determined by means of a checklist obtained from the causes of hypokalemia as mentioned in Harrison's Principles of Internal Medicne, 18th edition. In case a cause was not mentioned in this

list but has been described and known in literature ro cause hypokalemia , it was also included as the possible underlying cause.

DATA ENTRY:

The data was entered in Epidata version 3.1 and analysis was done using the SPSS software.

STATISTICAL ANALYSIS:

Sample Size

The sample size to show proportion of patients with hypokalemia was found to be 200 subjects with 95% confidence intervals and 5% precision with an anticipated proportion of about 15%

(A retrospective pilot analysis was done prior to the calculation of sample size using medical records of patients admitted in Christian Medical College and hospital, Vellore from 01/04/2013 to 31/03/14 which showed that the total number of adult patients admitted in the hospital with hypokalemia on the day of admission was 15,521; Total adult in patient population during the same time was 1,01,631. Hence, the proportion of patients with hypokalemia during this time period was 15.2 %)

Outcome measures:

The proportion of hypokalemia was calculated using the frequency and then expressed in percentage. 95% confidence interval for the proportion was calculated. The causes of hypokalemia, based on the assessment of the treating physician, were also calculated and expressed as percentages.

The association of hypokalemia and the causes of hypokalemia was assessed using chi-square test for categorical variables and independent t-test was used to compare the means of continuous variables with the presence or absence of hypokalemia and the causes of hypokalemia

Median time to mortality was compared across the groups using Tarone Ware test. Cox Proportional regression was planned to be done to compare the median time adjusting for any other factors.

The variables which were found significant in the chi-square or independent t-test were planned to be considered for multivariate analysis by performing logisitic regression.

The risk factors (use of inciting agents) for hypokalemia were also planned to be assessed using logistic regression after selecting the variables which were found to be significant from bivariate analysis.

RESULTS

Table 4: Demographic characteristics

	Cases (n=181)	%	Control (n=20)	%
Age (Mean)	50		48	
Age Groups (years)				
18-28	19	10.5	04	20
28-38	28	15.5	04	20
38-48	36	19.9	00	00
48-58	28	15.5	05	25
>58	70	38.7	07	35
Gender				
Male	110	60.8	13	65
Female	71	39.2	07	35
Medicine Unit				
I	38	21	04	20
II	40	22.1	04	20
III	40	22.1	06	30
IV	26	14.4	02	10
V	37	20.4	04	20
Occupation				
Housewife	54	29.8	03	15

Labourer	53	29.3	03	15
Student	07	3.9	03	15
Business	18	9.9	01	05
Farmer	21	11.6	02	10
Others	28	15.5	08	40
State				
Tamil Nadu	121	66.9	11	55
Andhra Pradesh	30	16.6	02	10
West Bengal	17	9.4	02	10
Others	13	7.2	05	25
Use of Inciting agents(last 3 months)				
Loop/Thiazide diuretics	16	8.8	00	00
Steroids	15	8.3	01	05
Inhaled Beta agonists	07	3.9	00	00
AAE	00	0	00	00
Insulin	13	7.2	02	10
Antibiotics	13	7.2	02	10
Cytotoxics	01	6.0	00	00
TAC	09	4.9	02	10
Hydroxycobalamine	00	0	00	00
Quetiapine overdose	00	0	00	00

Verapamil overdose	00	0	00	00

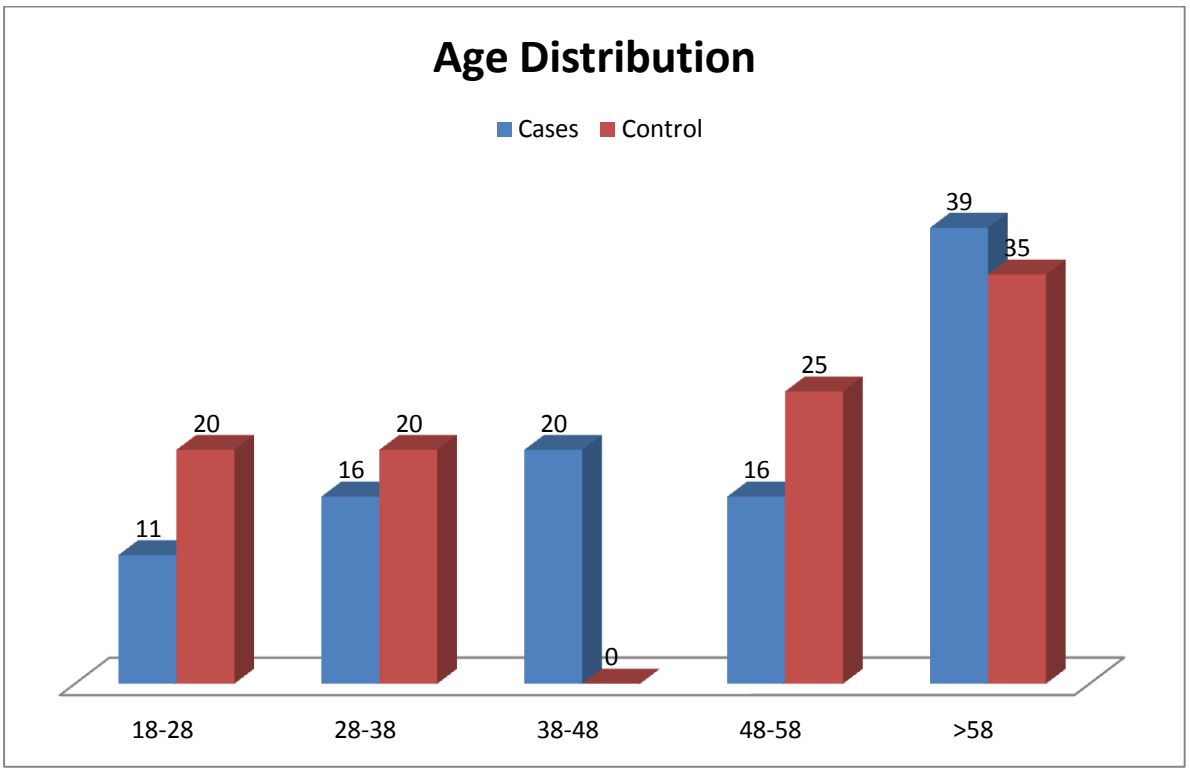


Figure 1: Proportion of patients among cases and control based on age distribution

X- axis: Percentage of patients; Y axis: Age distribution in years

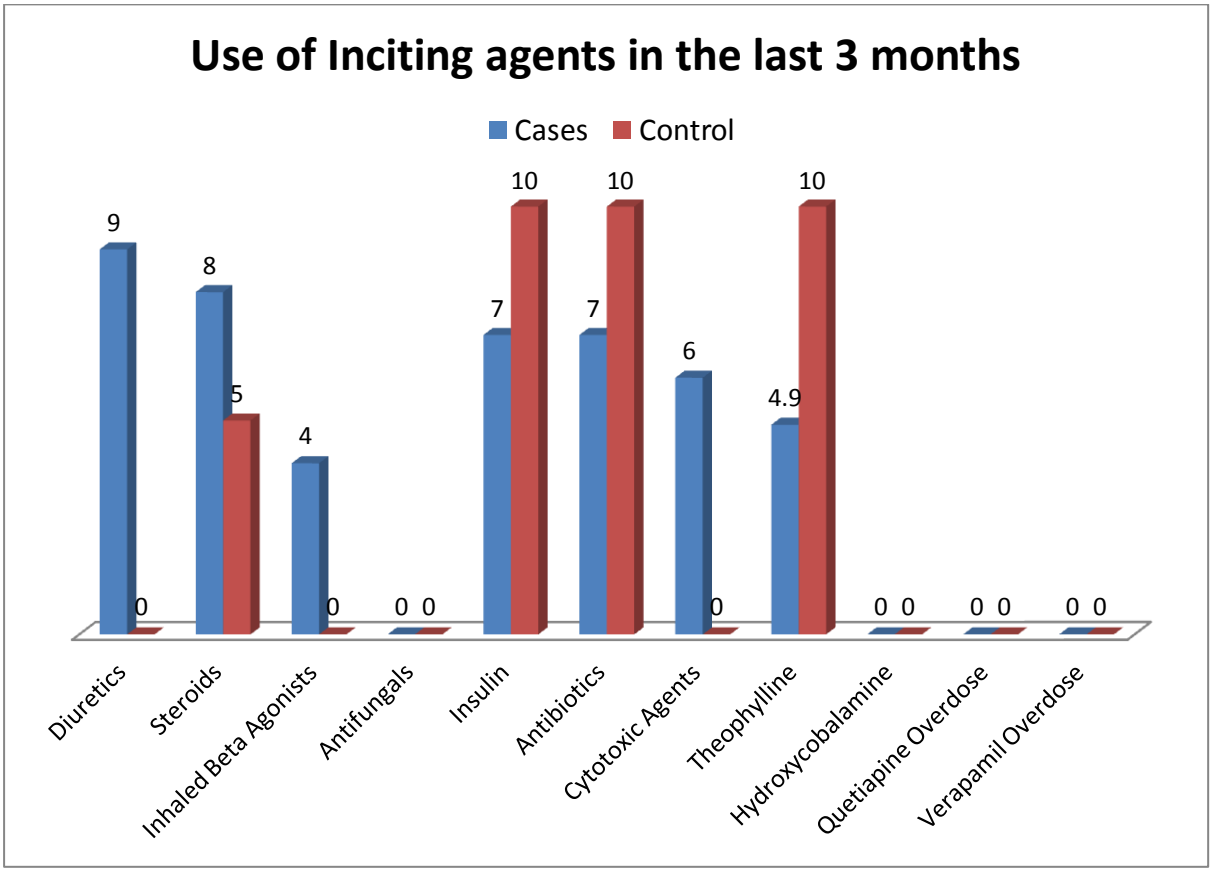


Figure 2: Bar chart showing the proportion of patients using inciting agents in the last 3 months among cases and control

X-axis: Proportion of patients; Y-axis: Inciting agent

Table 5: Comorbidities in Cases and Control groups along with their frequencies

Comorbidity	Cases (n=181)	(%)	Control (n=20)	(%)
Diabetes Mellitus	69	38.1	8	40
Hypertension	61	33.7	7	35
Smoking	27	14.9	4	20
Alcohol	26	14.4	4	20
Ischemic Heart Disease	13	7.2	1	5
Cerebrovascular Accident	11	6.1	0	0
Leukemia	0	0	0	0
Heart Failure	3	1.7	0	0
Peripheral Vascular Disease	2	1.1	1	5
COPD	9	5.0	1	5
CKD	5	2.8	1	5
Liver Disease	0	0	0	0
Dementia	0	0	0	0
Lymphoma	1	0.6	0	0

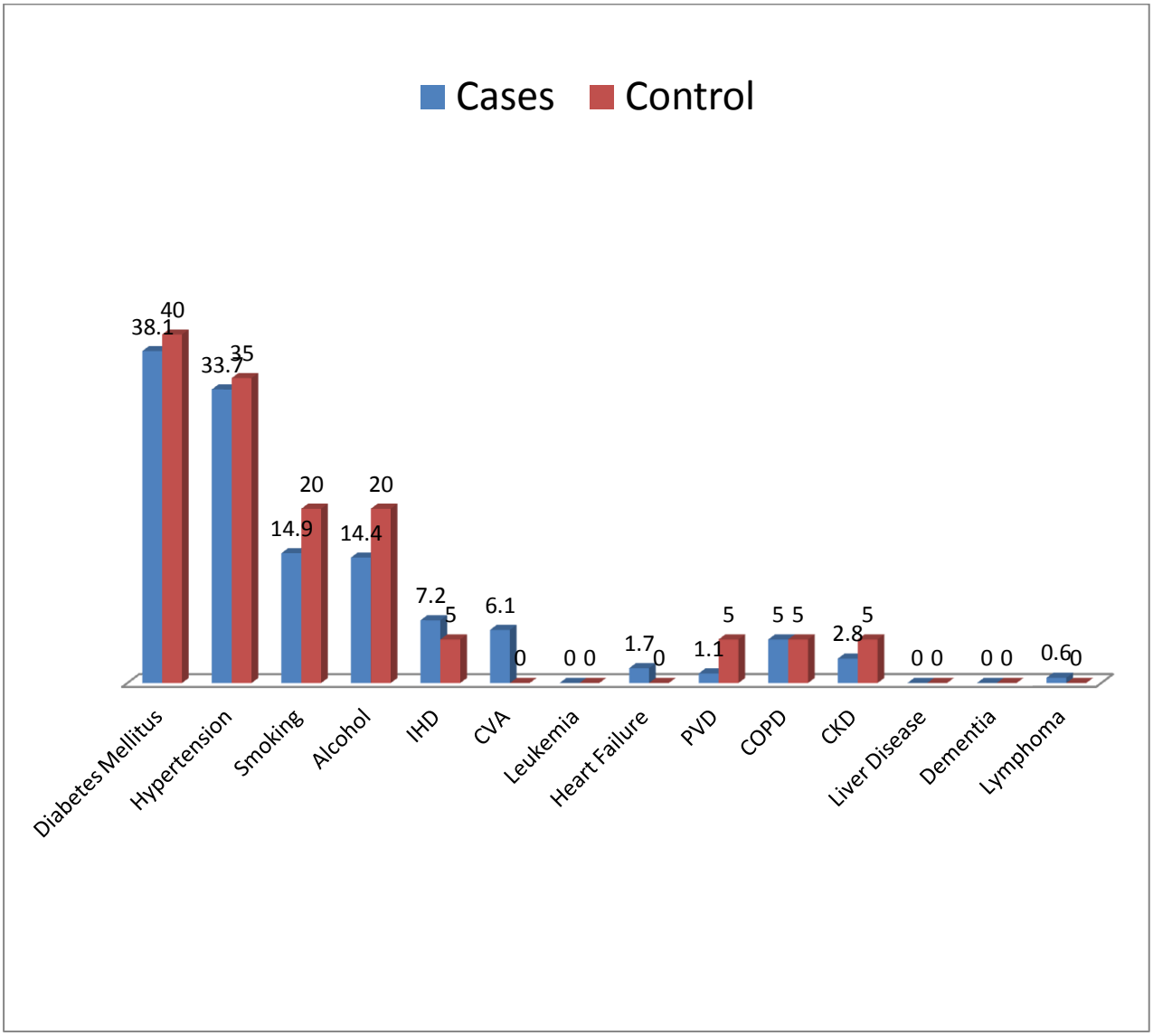


Figure 3: Proportion of co-morbidities in cases and control

IHD: Ischemic heart disease; CVA: Cerebrovascular accident; PVD: Peripheral Vascular Disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic Kidney Disease

Table 6: Co morbidities in Cases based on severity of hypokalemia

Comorbidities	Mild(n=140)	%	Moderate(n=30)	%	Severe(n=11)	%
Diabetes Mellitus	56	40	9	30	4	36.4
Hypertension	49	35	8	26.7	4	36.4
Smoking	16	11.4	8	26.7	4	36.4
Alcohol	22	15.7	3	10	1	9.0
IHD	11	7.9	2	6.7	0	0
CVA	8	5.7	3	10	0	0
Leukemia	0	0	0	0	0	0
Heart Failure	3	2.1	0	0	0	0
PVD	1	0.7	0	0	0	0
COPD	6	4.3	2	6.7	1	9.0
CKD	4	2.9	0	0	1	9.0
Liver Disease	1	0.7	0	0	0	0
Dementia	0	0	0	0	0	0
Lymphoma	0	0	0	0	1	9.0

IHD: Ischemic heart disease; CVA: Cerebrovascular Accident; PVD: Peripheral Vascular disease; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease

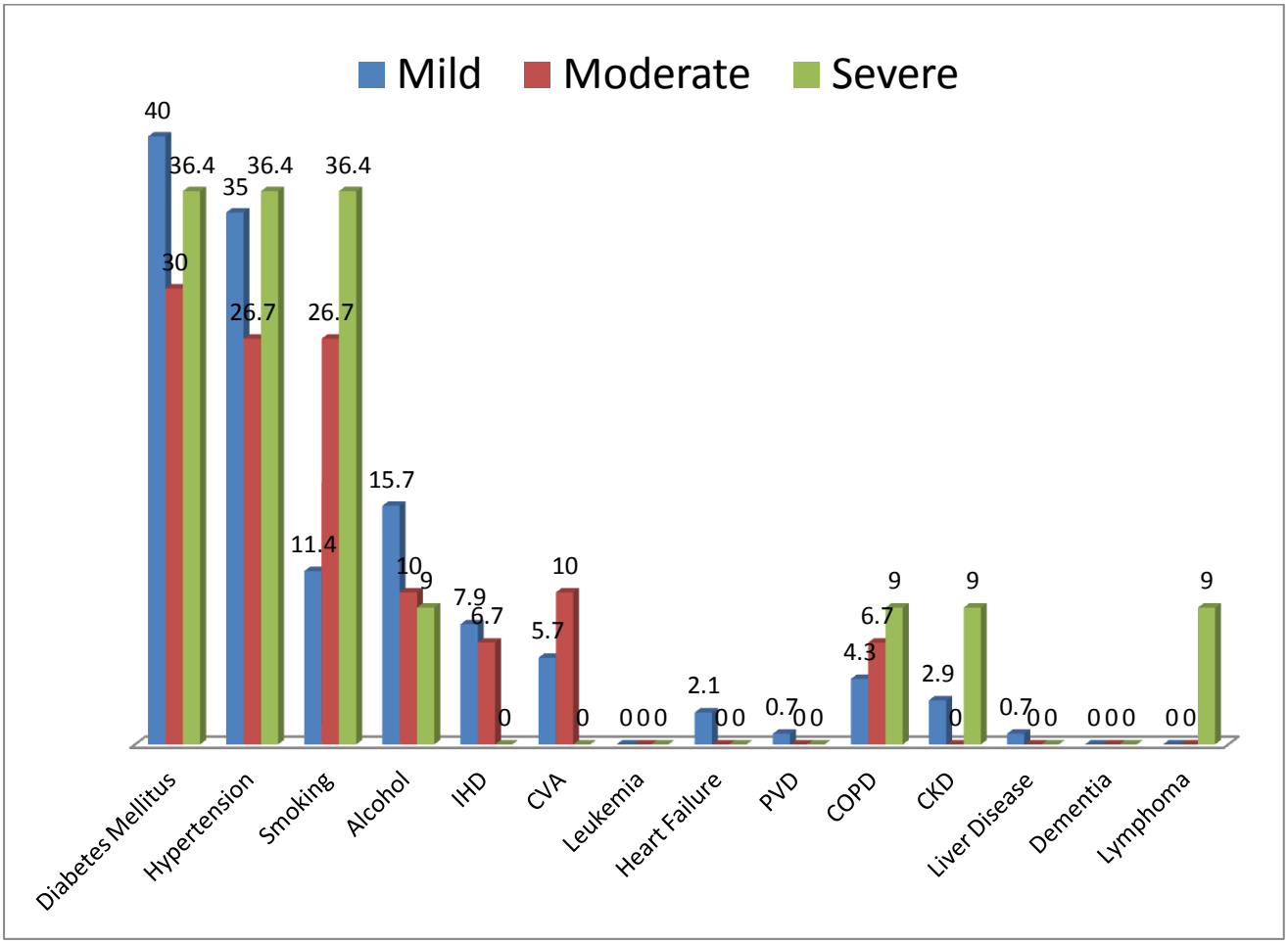


Figure 4: Co-morbidities in the different classes of severity of hypokalemia expressed as percentage

IHD: Ischemic heart disease; CVA: Cerebrovascular accident; PVD: Peripheral Vascular Disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic Kidney Disease

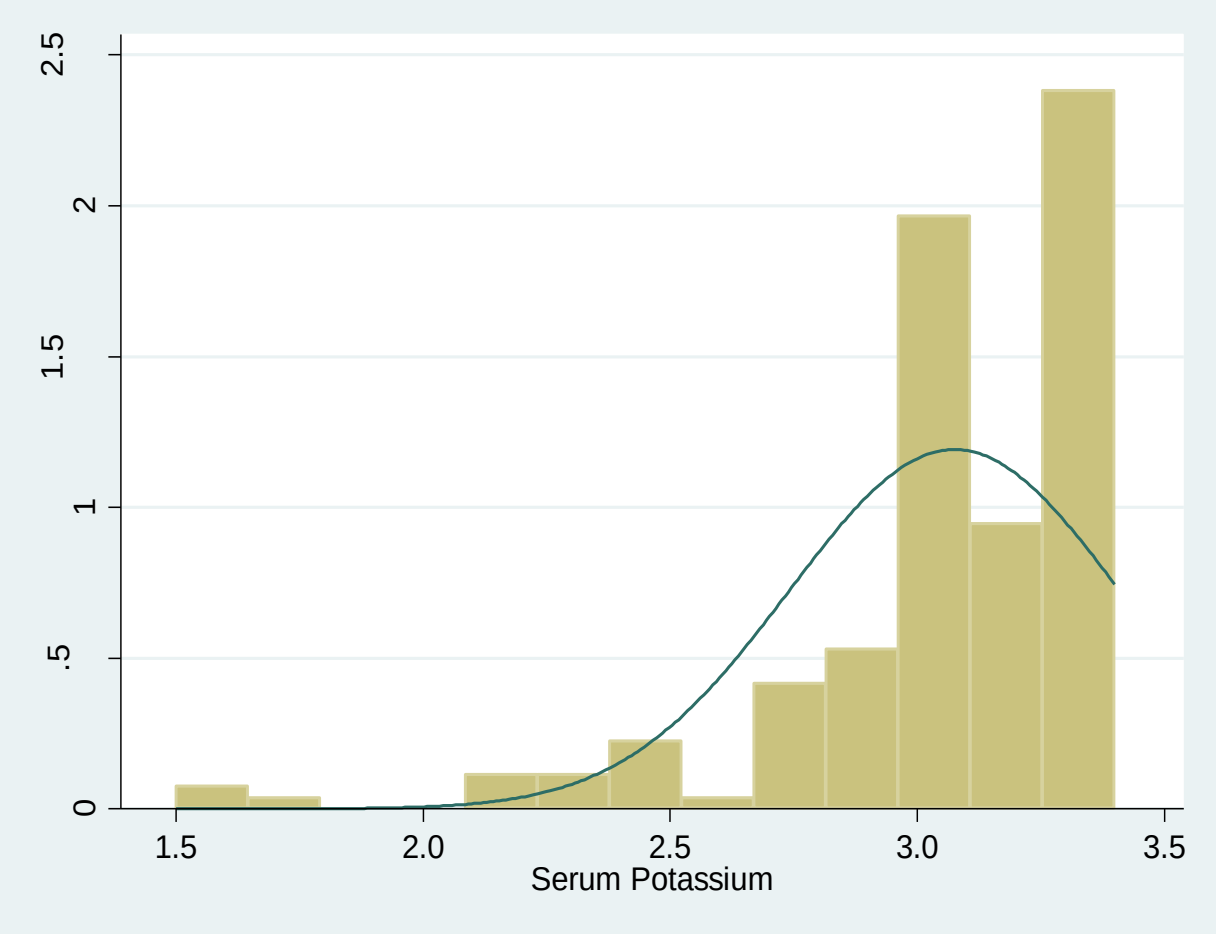


Figure 5: Histogram showing the distribution of serum potassium level among cases

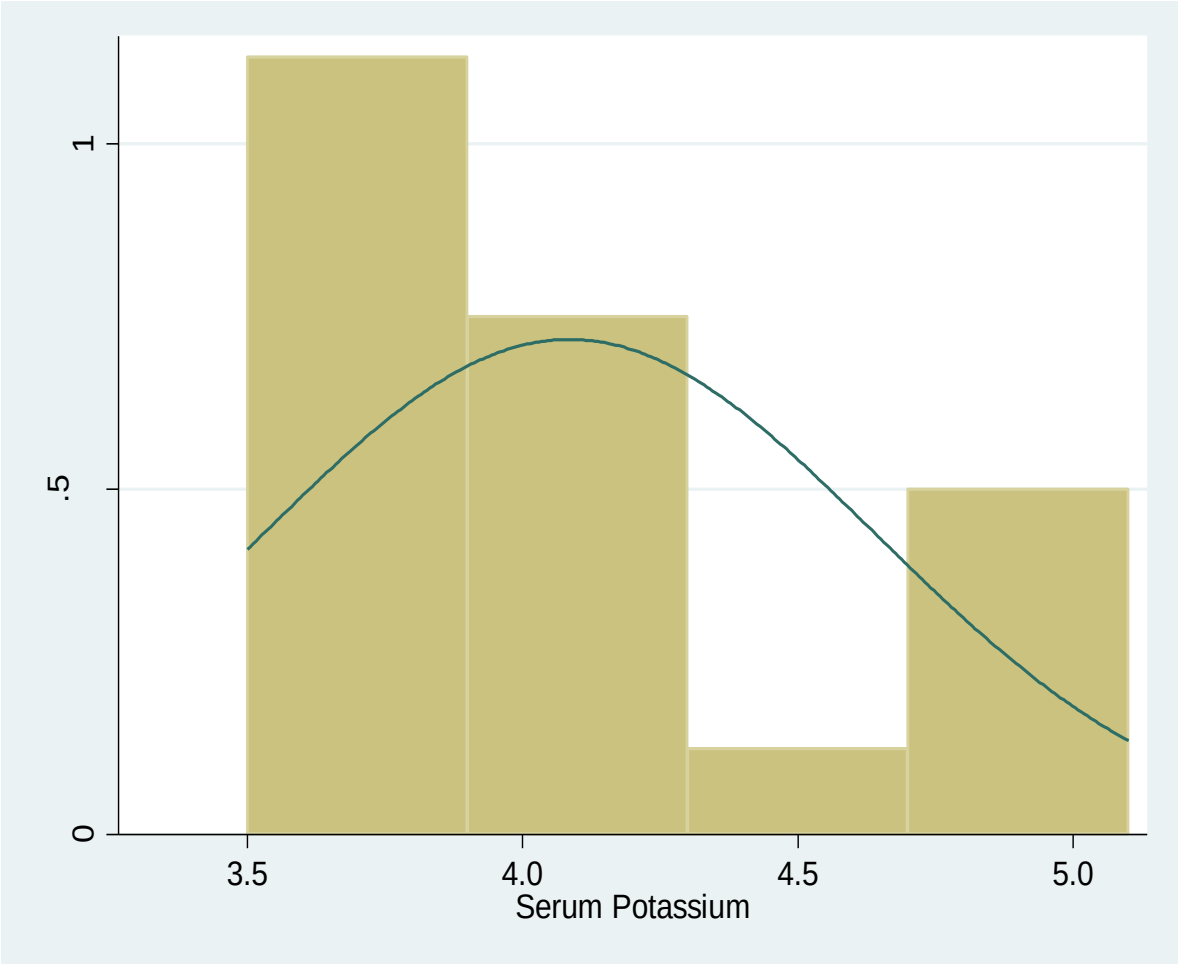


Figure 6: Histogram showing the distribution of serum potassium among controls

PROPORTION OF PATIENTS WITH HYPOKALEMIA

Table 8: Proportion of patients with hypokalemia

Number of patients in the medical wards	Hypokalemics at day 1 of admission	Proportion(%)	95% Confidence Interval
377	181	48	0.42-0.53

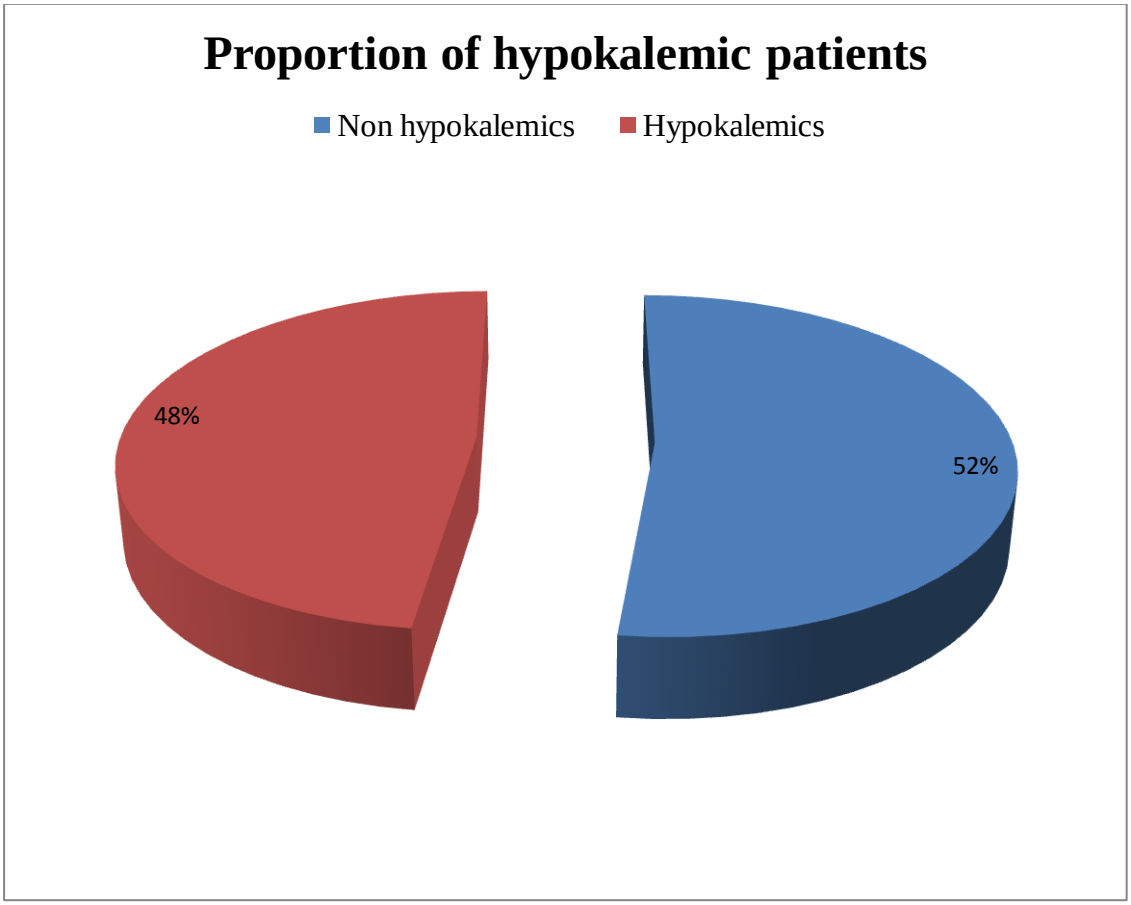


Figure 7: Proportion of patients admitted with hypokalemia at day 1 of hospital admission

Table 9: Proportion of patients based on severity of hypokalemia among the total number of patients admitted

Hypokalemia	Proportion(%)	95% Confidence Interval
Mild	37	0.32-0.42
Moderate	8	0.05-0.11
Severe	3	0.01-0.05

Table 10: Proportion of patients based on severity among patients who had hypokalemia

Severity of hypokalemia	Proportion (%)	95% Confidence Interval
Mild	77.3	0.70-0.83
Moderate	16.6	0.11-0.22
Severe	0.06	0.03-0.10

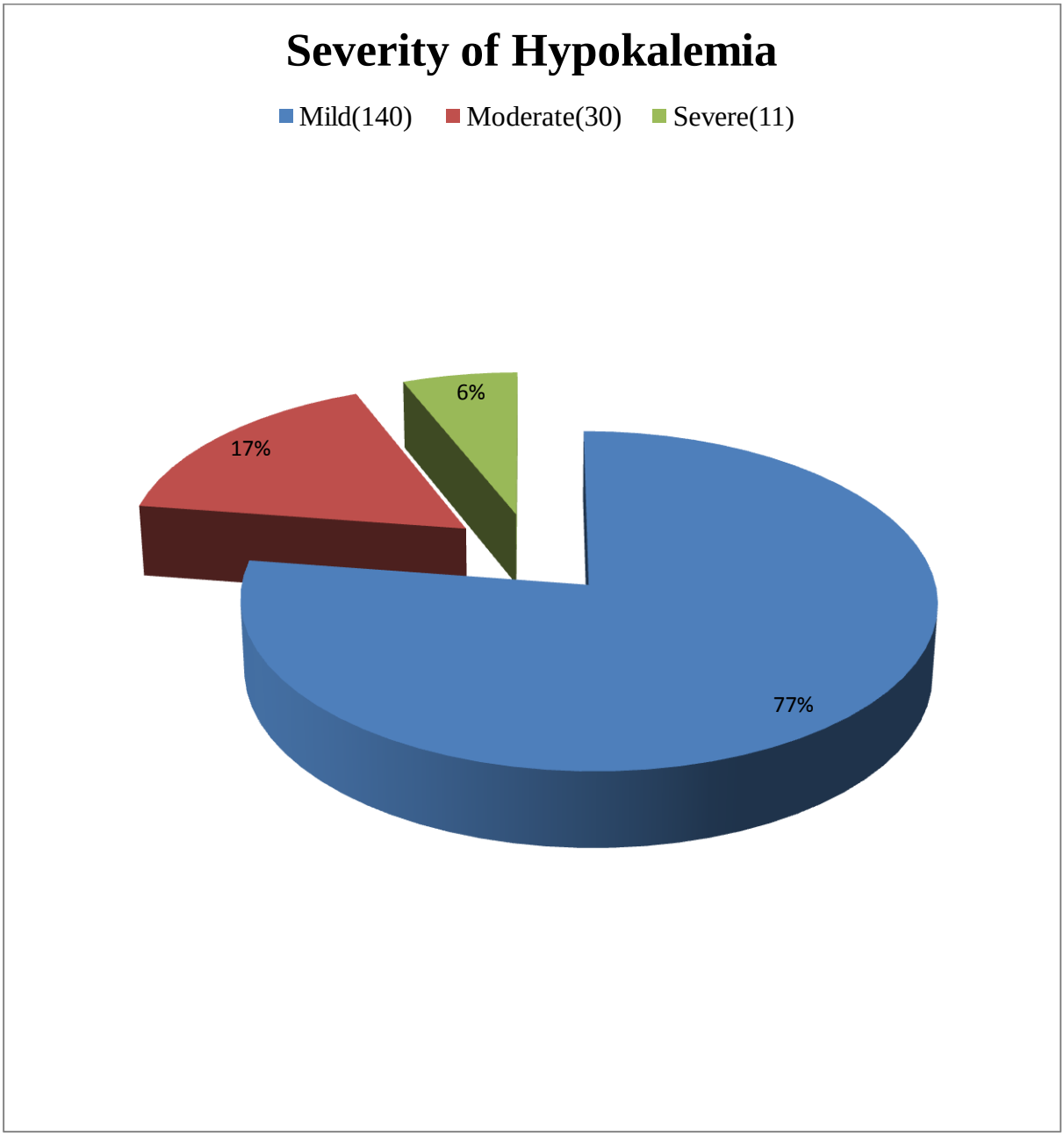


Figure 8: Pie chart showing the number and proportion of patients in accordance to the severity of hypokalemia

THE UNDERLYING CAUSES FOR HYPOKALEMIA (based on the treating physician's assessment)

Table 11: Most probable underlying causes for hypokalemia

Underlying cause	Frequency	%
Vomiting	61	33.7
Loose stools	28	15.5
Cerebrovascular accident	26	14.4
Magnesium deficiency	12	6.6
Diuretics	14	7.7
Deriphylline	2	1.1
Distal RTA	1	0.6
Proximal RTA	2	1.1
Digoxin	2	1.1
Mineralocorticoid excess	1	0.6
Steroids	10	5.5
Penicillin derivatives	3	1.7
Insulin	11	6.1
Metabolic alkalosis	5	2.8
Osmotic diuresis	13	7.2
Inhaled Beta agonist	5	2.8
Chronic kidney disease	21	11.6
Undetermined	146	80.7

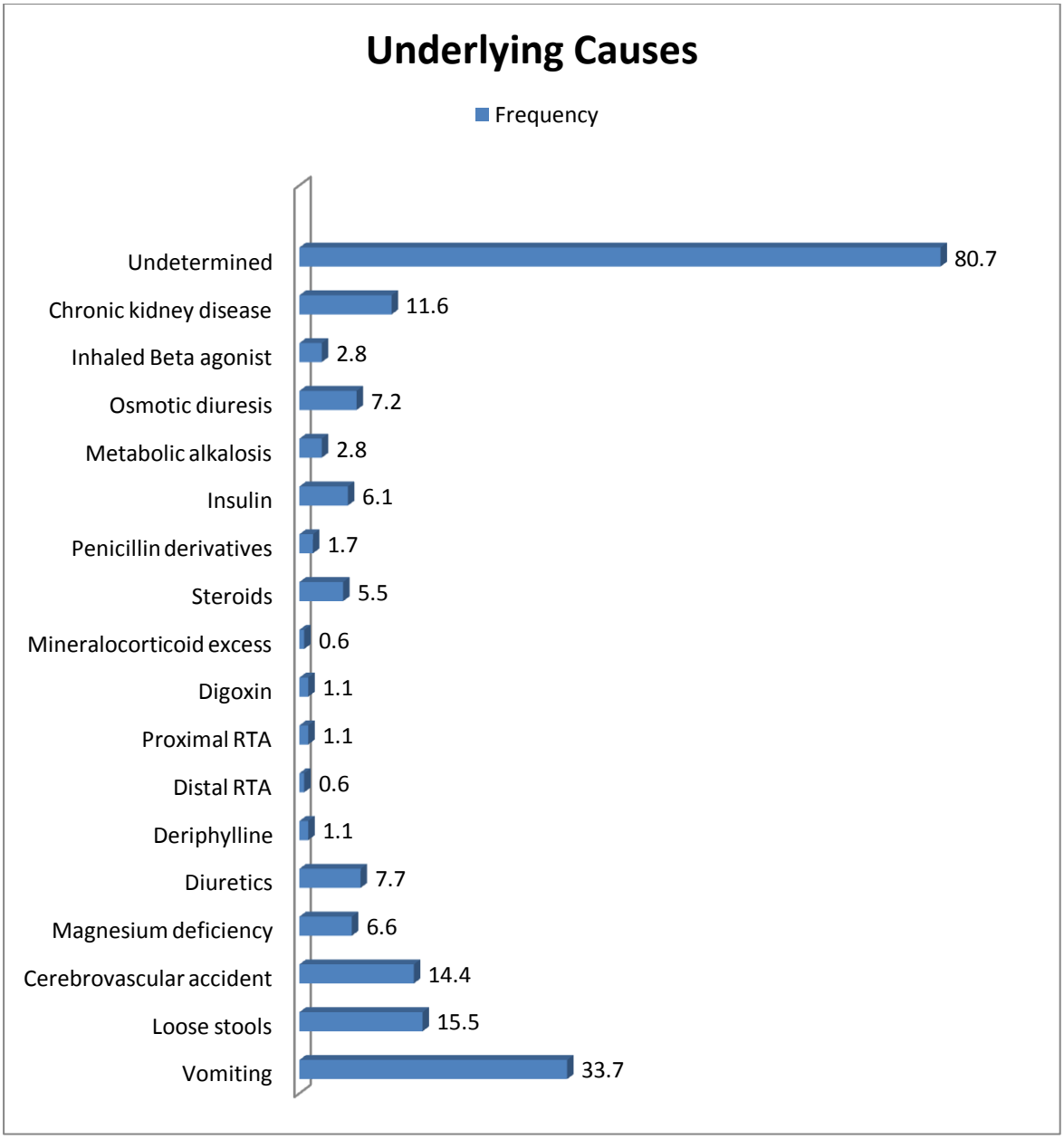


Figure 9: The possible underlying causes for hypokalemia at day 1 of hospital admission in percentage

SWN: salt wasting nephropathy; IBA: inhaled beta agonist; RTA: Renal tubular acidosis; Mg: Magnesium; CVA: Cerebrovascular accident

Table 12: Mortality among cases and control groups

	Cases						Control	%
	Mild	%	Moderate	%	Severe	%		
Discharged	132	94	30	100	10	90.9	19	95
Death	8	6	0	0	1	9.1	1	5

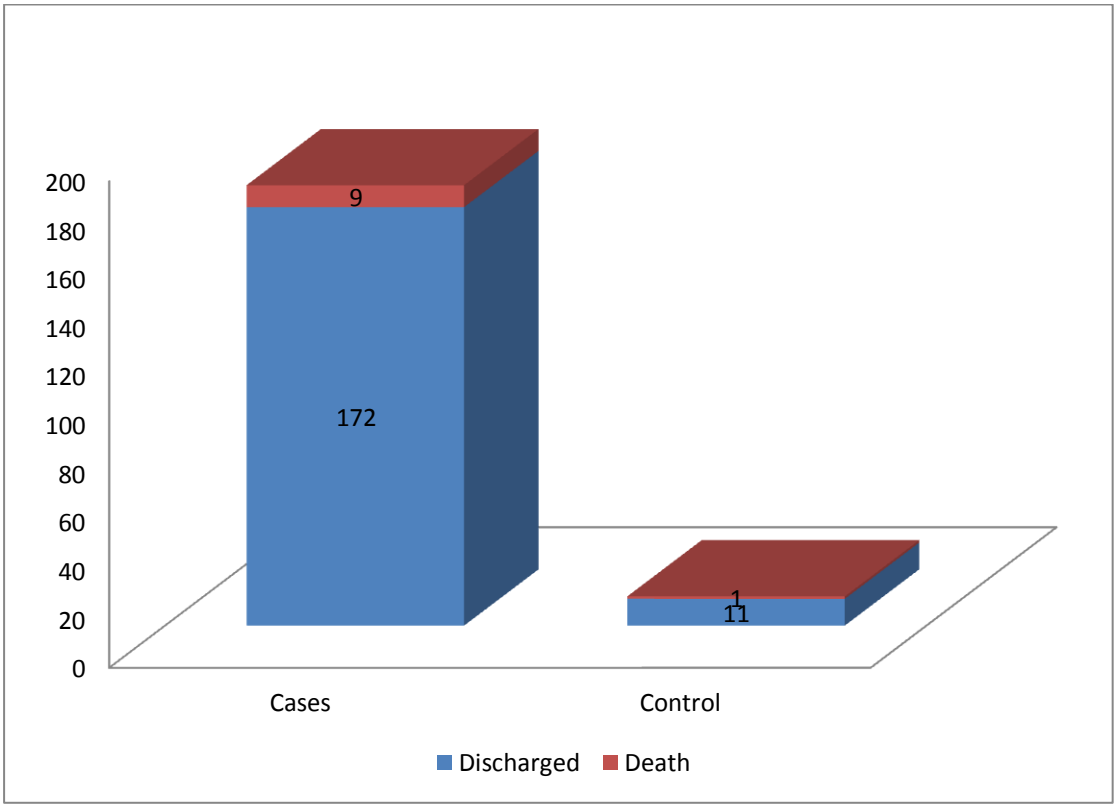


Figure 10: Mortality among cases and control

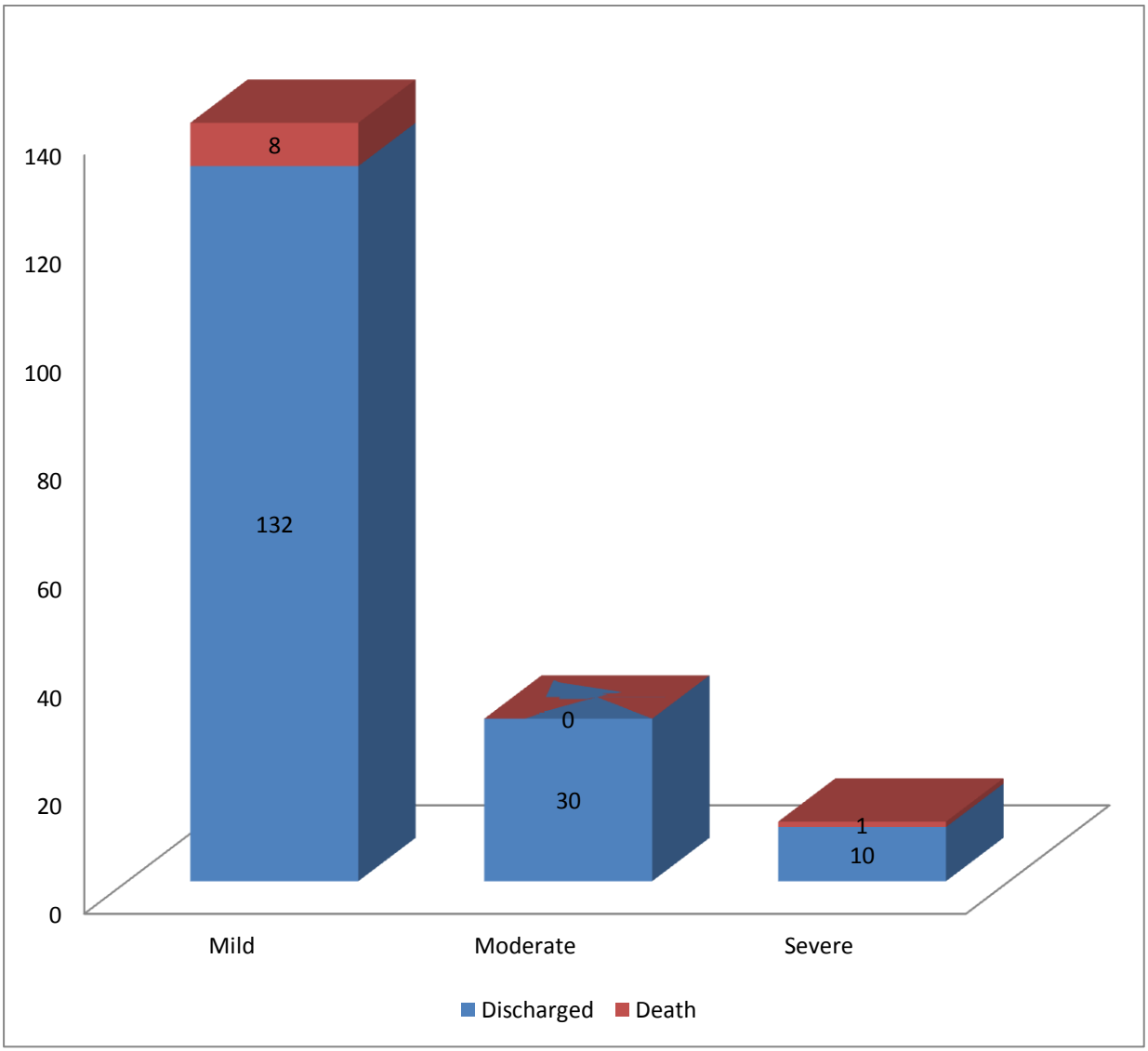


Figure 11: Mortality in the various degrees of severity of hypokalemia

Table 13: Mortality Rate among cases and control groups

	Mortality Rate(%)	P value
Cases	4.4	0.631
Control	0.4	0.631

Table 14: Mortality Rate among various degrees of severity of hypokalemia

Severity of Hypokalemia	Mortality Rate(%)	P value
Mild	3.9	0.246
Moderate	0	-
Severe	0.04	0.246

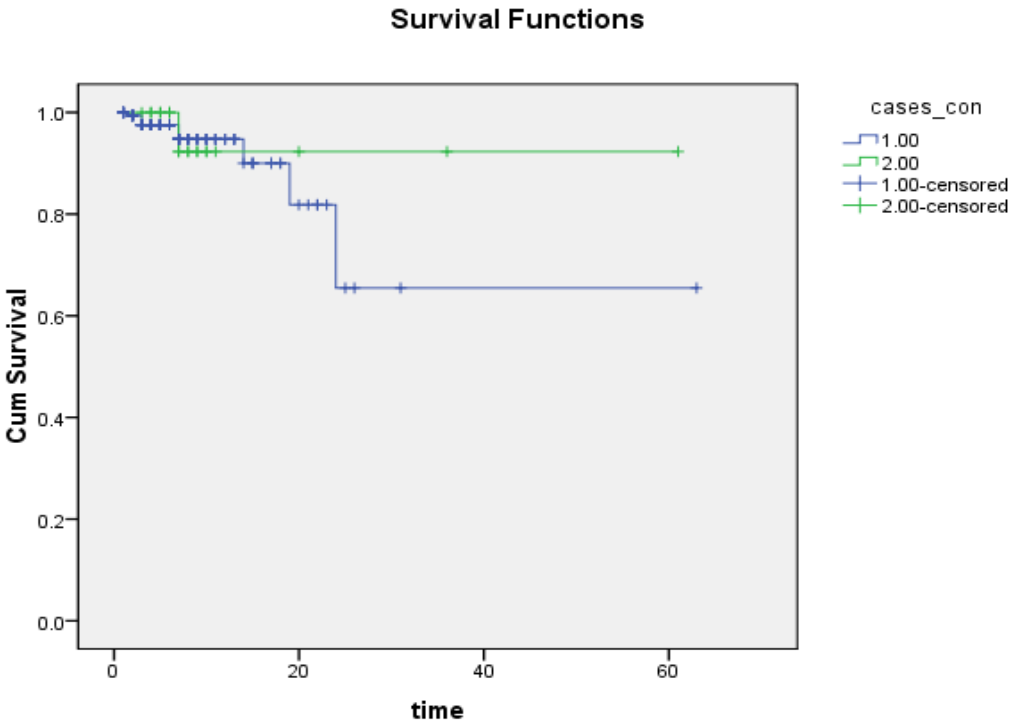


Figure 12: Survival plot in cases and control (1= cases; 2= control)

'Censored' implies, the ones who were living were followed up till the point of discharge and not thereafter.

Table 15: Mean survival time in cases and control

Category	Mean Survival time (Days)	95 % CI
Cases	47.65	34.5-60.7
Control	56.84	49.0-64.6

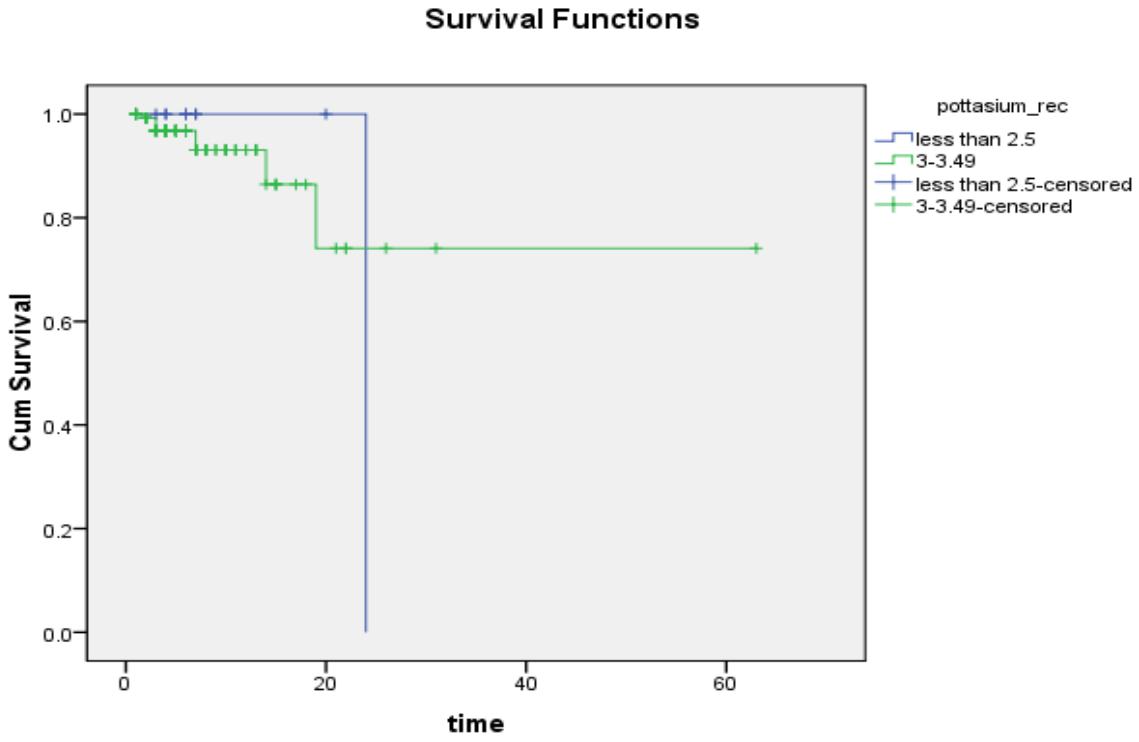


Figure 13: Survival plot in various groups of severity of hypokalemia 'Censored' implies, the ones who were living were followed up till the point of discharge and not thereafter

Table 16: Mean Survival time in accordance to severity of hypokalemia

Severity of Hypokalemia	Mean Survival time (Days)	95% CI
Mild	44.5	29.5-59.5
Moderate*	-	-
Severe	24.0	24.0-24.0

*Moderate hypokalemics did not have any death

HYPOKALEMIA AND COMORBIDITIES

Table 17: Univariate analysis of hypokalemia and comorbidities in cases and control

Comorbidity	Cases (n=181)	(%)	Control (n=20)	(%)	P value
Diabetes Mellitus	69	38.1	8	40	1.000
Hypertension	61	33.7	7	35	1.000
Smoking	27	14.9	4	20	0.521
Alcohol	26	14.4	4	20	0.050
Ischemic Heart Disease	13	7.2	1	5	1.000
Cerebrovascular Accident	11	6.1	0	0	0.605
Leukemia	0	0	0	0	1.000
Heart Failure	3	1.7	0	0	1.000
Peripheral Vascular Disease	2	1.1	1	5	0.271
COPD	9	5.0	1	5	1.000
CKD	5	2.8	1	5	1.000
Liver Disease	0	0	0	0	1.000
Dementia	0	0	0	0	1.000

Lymphoma	1	0.6	0	0	1.000

IHD: Ischemic heart disease; CVA: Cerebrovascular Accident; PVD: Peripheral Vascular disease; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease

SEVERITY OF HYPOKALEMIA AND COMORBIDITIES

Table 18: Univariate analysis of the severity of hypokalemia and comorbidities

Comorbidity	Mild n 140	%	Moderate n 30	%	Severe n11	%	P
Diabetes Mellitus	56	40	9	30	4	36.4	0.609
Hypertension	49	35	8	26.7	4	36.4	0.738
Smoking	16	11.4	8	26.7	4	36.4	0.794
Alcohol	22	15.7	3	10	1	9.0	0.789
IHD	11	7.9	2	6.7	0	0	1.000
CVA	8	5.7	3	10	0	0	0.482

Leukemia	0	0	0	0	0	0	1.000
Heart Failure	3	2.1	0	0	0	0	1.000
PVD	1	0.7	0	0	0	0	1.000
COPD	6	4.3	2	6.7	1	9.0	0.517
CKD	4	2.9	0	0	1	9.0	0.300
Liver Disease	1	0.7	0	0	0	0	1.000
Dementia	0	0	0	0	0	0	1.000
Lymphoma	0	0	0	0	1	9.0	1.000

IHD: Ischemic heart disease; CVA: Cerebrovascular Accident; PVD: Peripheral Vascular disease; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease

USE OF INCITING AGENTS AND HYPOKALEMIA

Table 19: Univariate analysis of use of inciting agent and hypokalemia

Agent	Cases(n=181)	%	Control(n=20)	%	P
Loop/Thiazide diuretics	16	8.8	00	00	0.377
Steroids	15	8.3	01	05	1.000
Inhaled Beta Agonists	7	3.9	00	00	1.000
Amphotericin B/Azoles/Echinocandins	00	0	00	00	-
Insulin	13	7.2	02	10	0.649
Antibiotics(Ampicillin, Caebenicillin, other penicillin, Gentamicin)	13	7.2	02	10	0.649
Cytotoxic Agents	01	6.0	00	00	1.000
Theophylline/Aminophylline /Caffeine	09	4.9	02	10	0.300
Hydroxycobalamine	00	0	00	00	-
Quetiapine overdose	00	0	00	00	-
Verapamil Overdose	00	0	00	00	-

USE OF INCITING AGENTS AND SEVERITY OF HYPOKALEMIA

Table 20: Univariate analysis of use of inciting agents in the last 3 months and severity of hypokalemia

Inciting Agent	Mild	%	Moderate	%	Severe	%	P
Diuretics	12	8.6	4	13.3	0	0	0.328
Steroids	11	7.9	2	6.7	2	18.2	0.675
IBA	5	3.6	1	3.3	1	9.1	0.543
Antifungals	0	0	0	0	0	0	-
Insulin	12	8.6	1	3.3	0	0	0.671
Antibiotics	11	7.9	2	6.7	0	0	0.919
Cytotoxics	1	0.7	0	0	0	0	1.000
HCB	0	0	0	0	0	0	-
Theophylline group	6	4.3	3	10	0	0	0.322
Quetiapine overdose	0	0	0	0	0	0	-
Verapamil Overdose	0	0	0	0	0	0	-

HYPOKALEMIA AND DOSE AND ROUTE OF POTASSIUM CORRECTION

Table 21: Dose and route of potassium correction in relation to the degree of hypokalemia

Degree of Hypokalemia	Route of Correction	Median (IQR) In grams	Standard deviation	P
Mild	Total(both iv and oral)	1.5 (0.0,5.6)	5.84	<0.001
	Intravenous	0.0 (0.0,3.0)	4.34	<0.001
	Oral	0.0 (0.0,0.0)	3.05	0.119
Moderate	Total(both iv and oral)	6.0 (2.9,14.9)	8.17	<0.001
	Intravenous	4.5 (1.5,10.5)	6.7	<0.001
	Oral	0.0 (0.0,0.13)	5.35	0.119
Severe	Total(both iv and oral)	15.0 (3.0,29.0)	18.61	<0.001
	Intravenous	9.0 (3.0,15.0)	8.47	<0.001
	Oral	0.0 (0.0,9.0)	15.32	0.119

iv : intravenous; IQR: inter quartile range

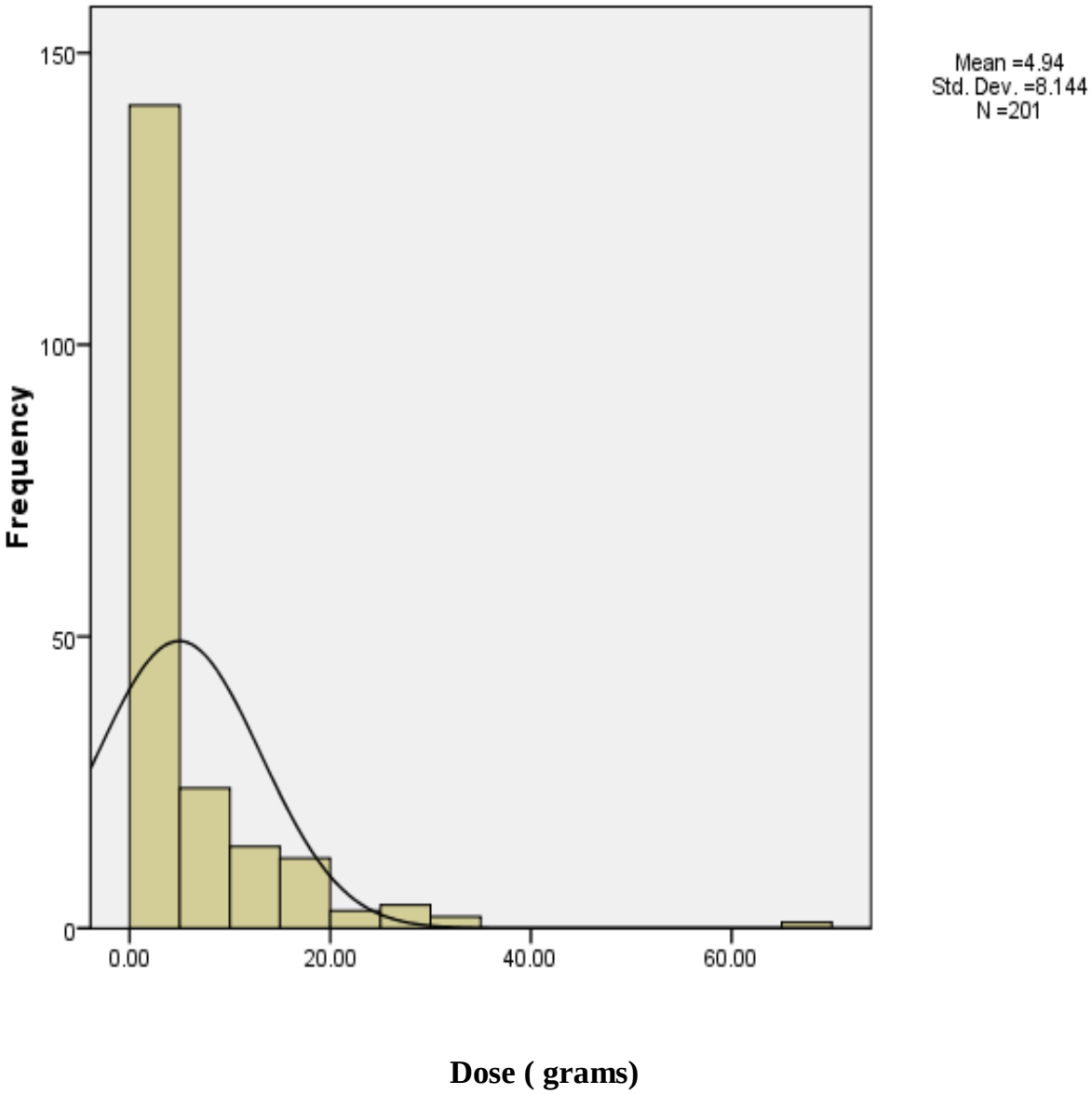


Figure 14: Total dose of potassium (both intravenous and oral) used for correction and their frequencies

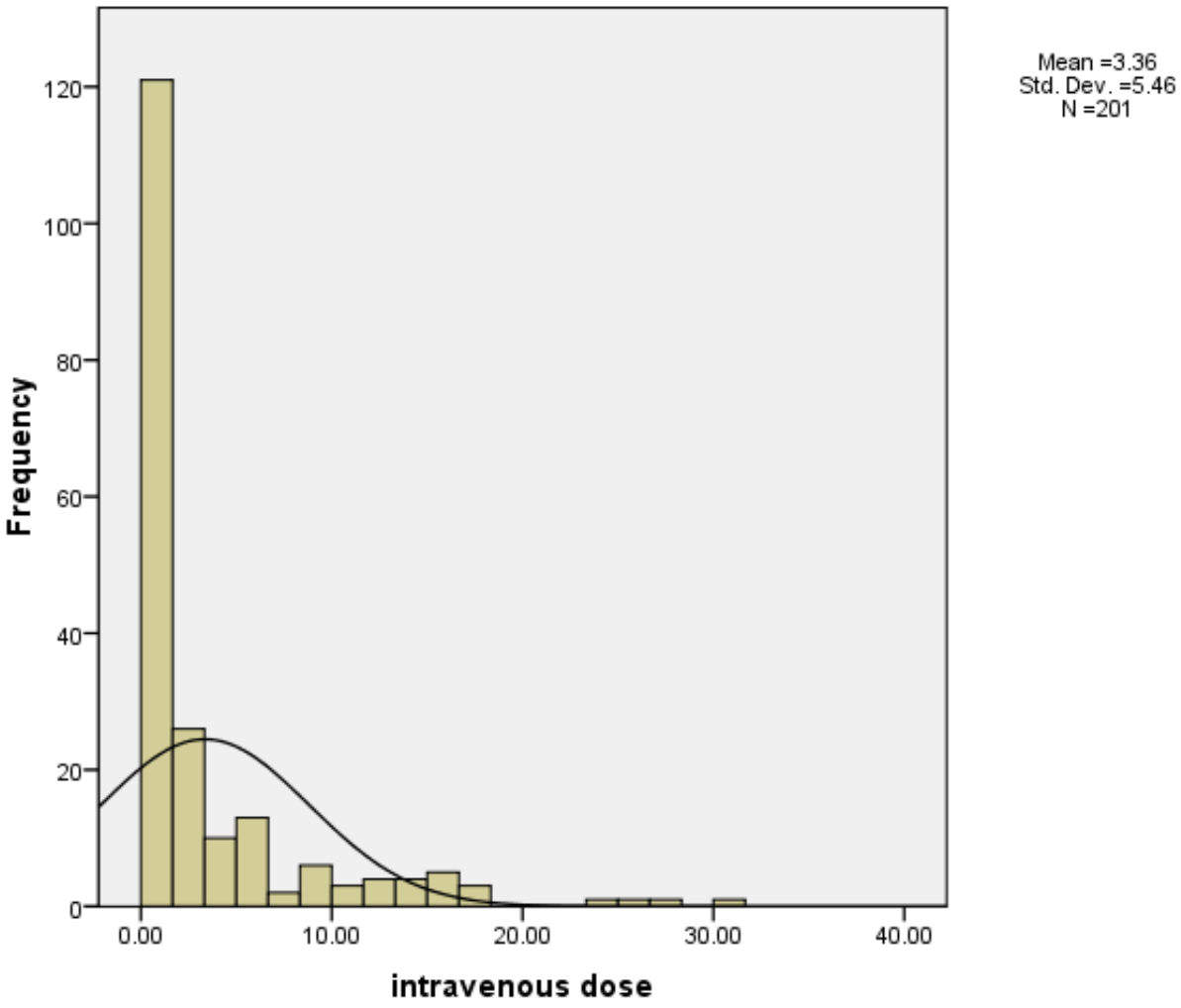


Figure 15: Intravenous dose of potassium used for correction in grams and their frequencies

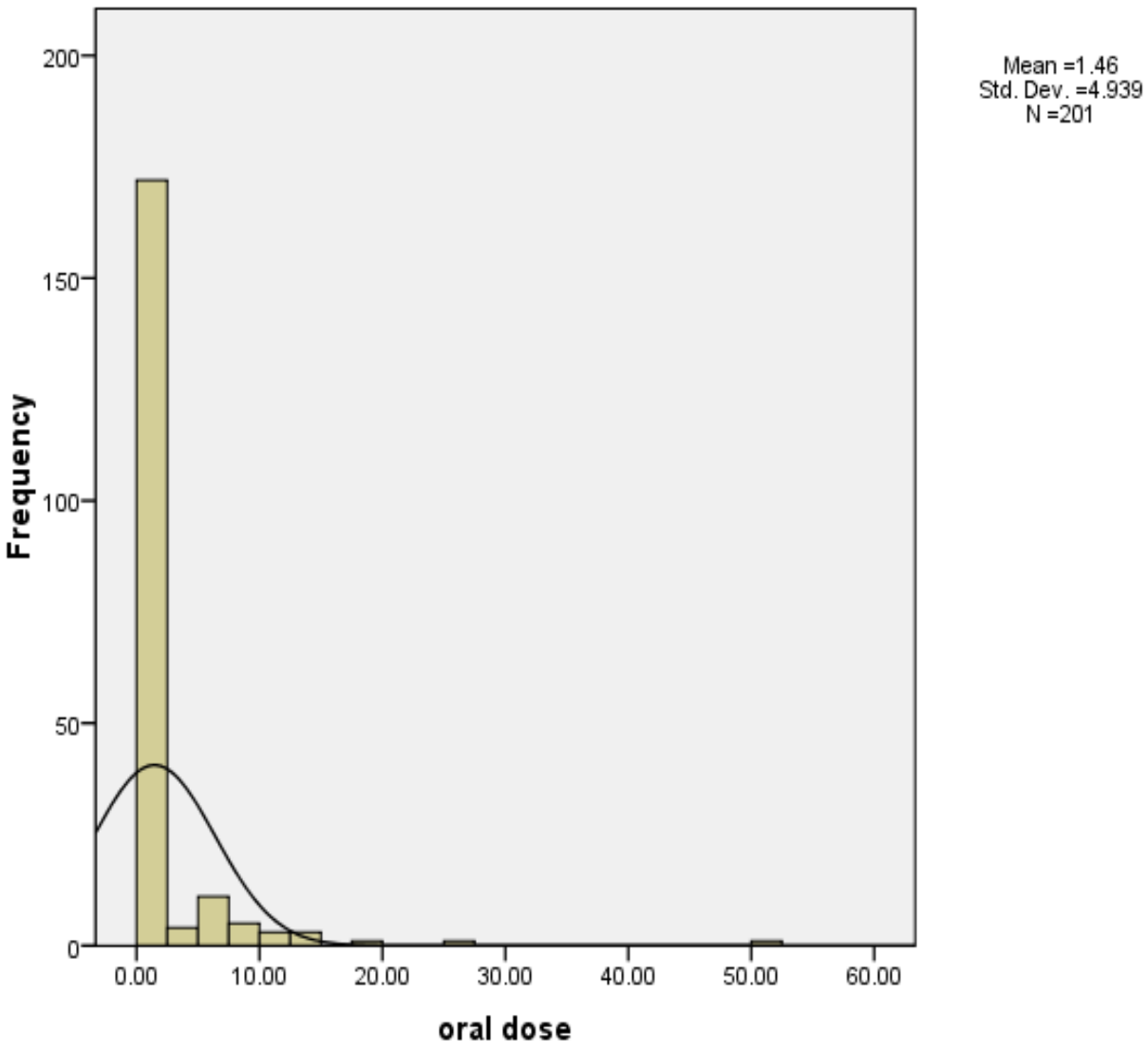


Figure 16: Oral dose of potassium used for correction in grams and their frequencies

HYPOKALEMIA AND DURATION OF POTASSIUM CORRECTION

Table 22: Analysis of hypokalemia and the duration of potassium correction

Degree of Hypokalemia	Median(IQR) In days	Standard deviation	P
Mild	0.17 (0.0,0.5)	1.45	<0.001
Moderate	0.50 (0.2,1.5)	1.77	<0.001
Severe	1.17 (0.2,3.4)	4.37	<0.001

IQR: inter quartile range

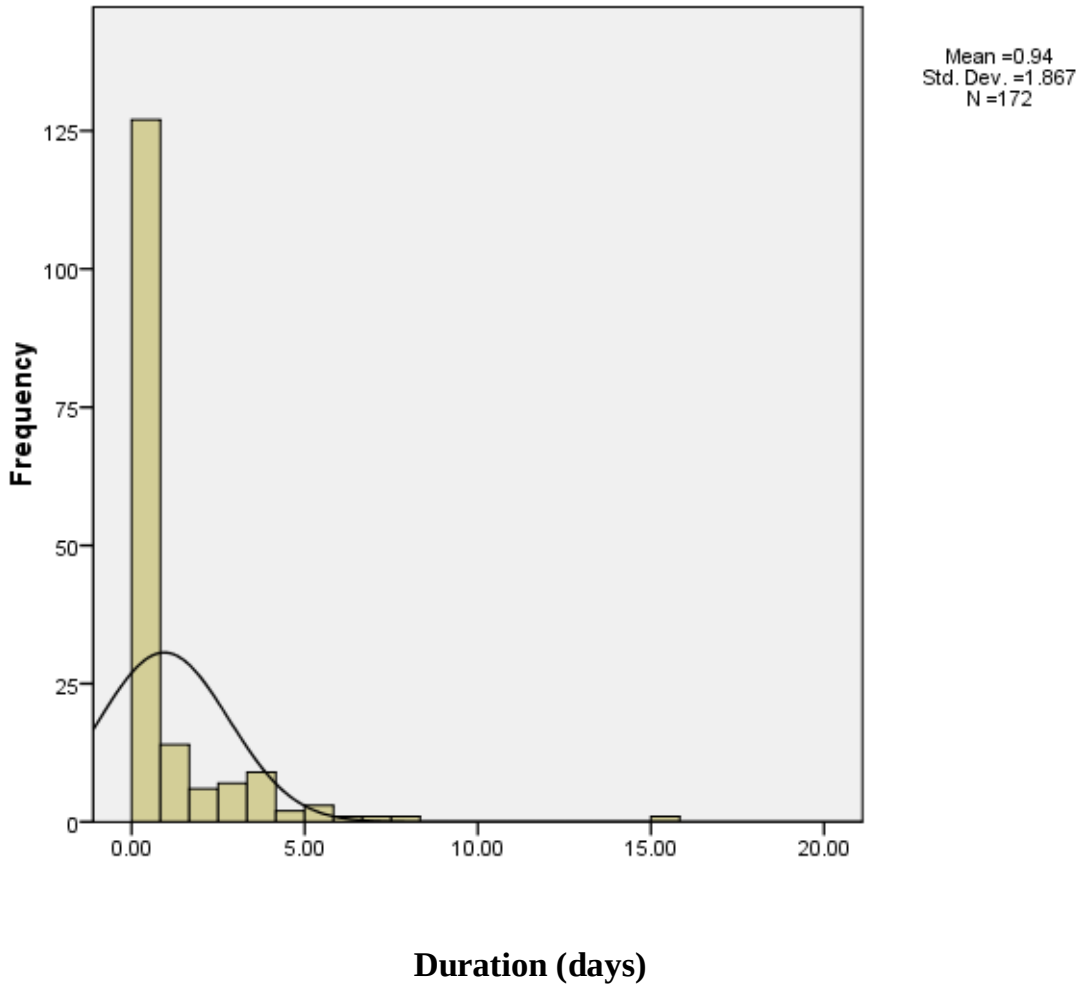


Figure 17: Duration of potassium correction and their frequencies

HYPOKALEMIA AND ECG CHANGES

Table 23: ECG changes among cases and controls

	Cases	%	Control	%	P
Frequency	108	60	12	60	0.003

Table 24: ECG changes among the various degrees of severity of hypokalemia

Degree of hypokalemia	Frequency	%	P
Mild	82	45.3	0.923
Moderate	18	9.9	0.923
Severe	8	4.4	0.923

Table 25: Frequencies of the types of ECG changes occurring among cases

Type of ECG change	Frequency	Percentage
Sinus tachycardia	37	20.4
Decreased T wave amplitude	59	32.6
Flattening of T wave	10	5.5
Inversion of T wave	10	5.5
PR prolongation	03	1.7
PR shortening	00	0
QT prolongation	43	23.8
U waves	02	1.1
VPCs	05	2.8
AF	07	3.9
Sinus arrhythmia	05	2.8
RBBB	02	1.1
LBBB	02	1.1
LVH	03	1.7
Junctional rhythm	01	0.5

Table 26: Frequencies of the types of ECG changes among controls

Type of ECG change	Frequency	Percentage
Sinus tachycardia	4	20
Decreased T wave amplitude	3	15
Flattening of T wave	0	00
Inversion of T wave	4	20
PR prolongation	0	00
PR shortening	1	05
QT prolongation	1	05
U waves	0	00
VPCs	0	00
AF	1	05
Sinus arrhythmia	1	05
RBBB	0	00
LBBB	0	00
LVH	0	00
Junctional rhythm	0	00

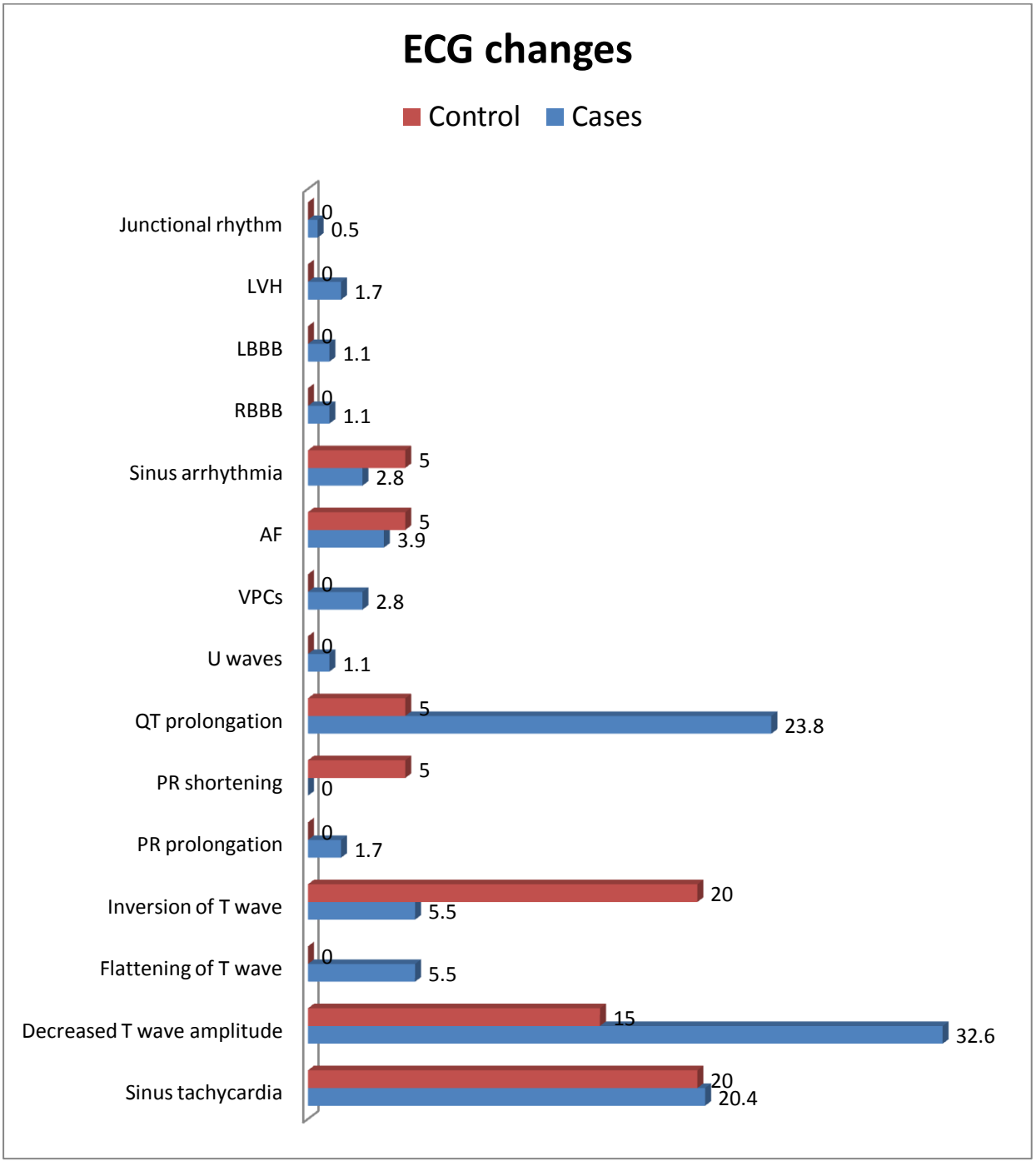


Figure 18: Frequencies of the types of ECG changes among cases and control groups in percentage

DISCUSSION

Demographic Characteristics

The patient population in this study had a mean age of 50 years among cases and 48 years among control group. Most of the patients in both the groups were more than 58 years of age (38.7% and 35 % in the cases and control groups respectively). There were no patients in the 38-48 years of age category among the control group. In the other categories of age, the percentage of patients in both the groups was similar. There were more males in both the groups than females which are in contrast to the Denmark and Glasgow studies where females were more than males.

Representation from each medical unit in the two groups was also similar. Maximum number of patients in both the groups was housewives followed by manual labourers and farmers as well as students. There were a few people who belonged to professions like police, artist, army, advocate, engineer, driver, clerk, mason, lecturer, homeopathic doctor, mechanic, nurse and salesman. Tamil Nadu was the state which was maximally represented followed by Andhra Pradesh and West Bengal in both the groups. Minor representations from other states like Jharkhand, Orissa, Bihar, Assam and Tripura were also there. There were 2 patients from other countries like Nepal and Bangladesh.

Proportion of patients with hypokalemia

The total admissions in the medical wards during the time period when this study was done was 377 out of which patients with hypokalemia on day 1 of hospital admission were 181. Therefore, the proportion of hypokalemics was 48% (CI 0.42-0.53) of the

total admissions in the general medical wards. This is higher than what has been described in earlier studies with the study in Glasgow showing the proportion as 21% , one done in Jakarta showing 23% and the Denmark study 16.8%.

Amongst the hypokalemics, the proportion of patients with mild, moderate and severe hypokalemia were 37% (CI 0.32-0.42), 8% (CI 0.05-0.11) and 3% (0.01-0.05) respectively. The proportion of patients in the severe category was similar to the Denmark study, which is definitely lower than the ones reported in earlier studies- 24.9% and 9.4%

The underlying causes of hypokalemia (based on treating physician's assessment)

The most common likely underlying cause for hypokalemia was undetermined comprising 80. 7% (possibilities were sweating and starvation). Amongst the named causes were gastrointestinal losses in the form of vomiting (33.7%) and loose stools (15.5%). Next to these was cerebrovascular accident (14.4%). Renal losses as the underlying cause were lesser in number, salt wasting nephropathy (11.6), osmotic diuresis(7.2%),proximal RTA (1.1%), distal RTA(0.6%). Among the drug related causes, diuretics were maximum (7.7%) followed by usage of insulin (6.1%) and steroids (5.5%)

Our study showed contrasting results compared to the Glasgow study where the most common likely underlying cause was found to be drugs (38%) with diuretics accounting for 62% cases, steroids 9 %, insulin 7% and hydroxycobalamine 7%. Gastrointestinal losses occurred only in 16.8% of cases. Renal losses accounted for 2.3% of cases.

Hypokalemia and Mortality

In this study, the mortality rate among cases was 4.4% and that among control was 0.4%. The difference in the mortality rates in between the two groups was not statistically significant. This could possibly be due to the fact that the control group had lesser number of patients compared to the cases group.

Among the various severity grades of hypokalemia, the mortality rate in the mild, moderate and severe hypokalemia groups were 3.9%, 0%, and 0.04% respectively. These differences were not statistically significant. This is in contrast to the results obtained from the Glasgow study which showed a statistically significant increased mortality among patients who had severe hypokalemia. The Denmark study too showed similar results but was not shown to be statistically significant. This was probably due to the number of fatal events being too less.

Mean survival time in the cases group was 47.65 days (CI 34.5-60.7) and in the control group was 56.84 days (49.0-64.8). The same was 44.5 (CI 29.5-59.5) and 24.0 (CI 24.0-24.0) in the mild and severe hypokalemia groups respectively. The moderate hypokalemia group did not have any deaths and hence, the mean survival time for this group was not calculated.

Hypokalemia and Co-morbidities

The distribution of co-morbidities among cases and control groups were mostly similar except cerebrovascular accident and heart failure which were more in the cases group. A univariate analysis of these co-morbidities did not show any statistically

significant difference between hypokalemics and non-hypokalemics as well as the various degrees of severity of hypokalemia.

Use of Inciting agents and hypokalemia

The most common inciting agent used within the last 3 months prior to hospital admission among hypokalemics was diuretics followed by steroids. The control group had more usage of insulin, antibiotics (penicillin derivatives) and theophylline group of drugs. A univariate analysis between the two groups did not show any statistically significant difference.

Among the various degrees of severity of hypokalemia, mild and moderate hypokalemics had more usage of diuretics whereas the severe hypokalemia group had more usage of steroids and no diuretics at all. A univariate analysis failed to reveal any statistically significant difference between the three groups.

Hypokalemia and dose, route of potassium correction

MILD HYPOKALEMIA

Among patients with mild hypokalemia, the total dose of potassium (intravenous plus oral) required for normalising serum potassium in 75% of patients was 5.6 grams.

Through the intravenous route, 75% of patients required a dose of 3.0 grams.

Through the oral route, 75% of patients did not require any oral correction at all.

The results were statistically significant for total and intravenous doses but not for the oral dose.

MODERATE HYPOKALEMIA

Among patients with moderate hypokalemia, 75% of patients required a total (intravenous plus oral) dose of 14.9 grams of potassium for normalising serum potassium.

For the intravenous route, 75% of patients needed 10.5 grams of potassium correction

For oral route, 75% of patients required 0.13 grams of potassium correction.

These results were again statistically significant for the total and intravenous doses but not for the oral dose.

SEVERE HYPOKALEMIA

In the severe hypokalemia group, 75 % of patients needed a total (intravenous plus oral) of 29.0 grams of potassium correction.

For intravenous route, 75% of patients required 15.0 grams of potassium, and for oral route, 75% of patients needed 9 grams of potassium for achieving eukalemia.

In this group too, the results were statistically significant in the total and intravenous doses but not for oral doses.

The amount of potassium required for correcting severe hypokalemia was about 7 times that required for correcting mild hypokalemia and 2.5 times that need for correcting moderate hypokalemia.

Intravenous dose needed to correct severe hypokalemia was about 2 times more than the moderate ones. Intravenous correction was hardly required in the mild hypokalemics.

Oral correction was not need in the mild hypokalemics, very minimally required in the moderate ones. For severe hypokalemics, oral doses were also required for correction along with intravenous doses.

Hypokalemia and duration of potassium correction

MILD HYPOKALEMIA

75% of patients required potassium correction for 0.5 days to achieve eukalemia.

MODERATE HYPOKALEMIA

75% of patients required potassium correction for 1.5 days to achieve eukalemia.

SEVERE HYPOKALEMIA

75% of patients required potassium correction for 3.4 days to achieve eukalemia.

All the above results were statistically significant

Hypokalemia and ECG changes

The ECG changes occurred in 60% of cases and 60% of control population. This result was statistically significant. The same occurring in the mild, moderate and severe hypokalemia groups were 45.3%, 9.9%, and 4.4% respectively stating that the same occurred more in the mild hypokalemia group. However, this finding was not statistically significant.

The most common ECG abnormality among patients with hypokalemia was decreased T wave amplitude followed by QT prolongation. Among the control group the most common ECG abnormality was sinus tachycardia followed by inversion of T wave. In literature, the earliest change that has been described to occur in hypokalemia is a decrease in the amplitude of T wave. Prolongation of QU interval has also been described (pseudo QT prolongation).

In this study, there did not seem to be difference in the number of ECG changes occurring among cases and control groups and though there were an increased number of ECG changes occurring among patients with mild hypokalemia than other degrees of severity of the same, this finding was not found to be statistically significant.

LIMITATIONS

This study had the following limitations:

1) Since this is an observational study, the findings of the same may have a likelihood of being biased. Therefore, further stronger studies need to be done to confirm the same.
2) The underlying cause was determined on a subjective assessment of the physician managing the patient in the medical wards. A more objective method like the measurement of trans tubular potassium gradient (ttkg) may need to be done in future studies to determine the same in individual patients.
3) The assessment of the ECG findings was done by the physicians in charge of the patient in the ward and there was no confirmation by an electro physiologist. Future studies may need confirmation of the same by such professional to eliminate any errors as well as bias.

CONCLUSIONS

The following conclusions are drawn from this study:

1) The proportion of patients with hypokalemia on day 1 of hospital admission was higher than previous studies. However, the proportion of severe hypoklaemics was similar to the Denmark study and lesser than earlier studies. The reason for this possibly could be that the previous studies community and hospital acquired hypokalemias together in their study. This differentiation was done in the Denmark study
2) The most common underlying cause of hypokalemia was undetermined causes seconded by gastrointestinal losses in the form of vomiting and loose stools. The use of objective methods like the determination of the transtubular potassium gradient (ttkg) in future studies may help to invade the territory of the undetermined causes as well as confirm the remaining causes which were subjectively assessed by the treating physician.
3) In this study, the mortality rate among hypokalemics was more than the non hypokalemics. However, this difference was not statistically significant. The mortality rate was, in contrast, more in the mild hypokalemics that the patients with severe hypokalemia. This difference too was not found to be statistically significant. These results obtained are in contrast to what was seen in the previous studies.
4) There was no statistically significant association established in between co-morbidities and hypokalemia.

5) Mild hypokalemics may not need any potassium correction or if at all they need, may need a very minimal dose of about 1.5 grams. Moderate hypokalemics may need minimal intravenous plus oral correction (about 4 times more than that needed for mild hypokalemia and 2.5 times less than that needed for severe hypokalemics) for normalising serum potassium with intravenous route as the main route of administration. Severe hypokalemics may need both intravenous and oral forms of potassium at higher doses for achieving eukalemia(10 times that needed for mild hypokalemia and 2.5 times that needed for moderate hypokalemia) with intravenous route as the main route of administration.
6) At an average mild hypokalemics become eukalemic within 4 hours, moderate hypokalemics within 12 hours and severe hypokalemics within 28 hours following potassium correction.
7) There was no difference in the number of patients showing ECG changes between hypokalemics and non hypokalemics but decreased T wave amplitude and QT prolongation was more common in hypokalemics. Occurance of u wave was seen only in hypokalemics
8) There was no significant association between use of inciting agents and hypokalemia as well as its severity.

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ANNEXURES

CLINICAL RESEARCH FORM

Annexure 1

Data Abstraction sheet.

Name: **Age:** **Sex**: M / F **DOA/1st visit**: …. /… /2015

Hosp No: **Occupation:** HW/Man labour/Student/Business/Farmer/…...

State: TN/AP/WB/…….. **Unit:** Med 1 / Med 2 /Med 3/ Med 4/ Med 5

Contact Number: **Address:**

Village/ town:

Comorbidity		Number of years	Comorbidity		Number of years
Diabetes mellitus	Yes/ No		Heart Failure	Yes/ No	
Hypertension	Yes/ No		Peripheral Vascular Disease	Yes/ No	
Smoking	Yes/ No		Chronic Obstructive Pulmonary Disease	Yes/ No	
Alcohol	Yes/ No		Chronic Kidney Disease	Yes/ No	
Ischaemic Heart Disease	Yes/ No		Liver Disease, Non alcohol related	Yes/No	
Cerebrovascular Accident	Yes/ No		Dementia	Yes/ No	
Leukemia	Yes/ No		Lymphoma	Yes/ No	

Use of inciting drugs in the past 3 months:

Loop diuretics / Thiazides	Yes / No
Steroids	Yes / No
Inhaled Beta 2 agonists	Yes / No
Amphotericin B/Azoles/Echinocandins(specify)	Yes / No
Insulin	Yes / No
Antibiotics (Ampicillin, Carbenicillin, other penicillin, gentamicin- specify name)	Yes / No
Cytotoxic agents (Cisplatin)	Yes / No
Hydroxycobalamine	Yes / No
Theophylline/aminophylline/ caffeine(specify)	Yes/ No
Quetiapine overdose	Yes/ No
Verapamil overdose	Yes/ No

Symptoms (duration)		Cardiovascular system	S1/S2/S3/S4 Murmurs Arrhythmias
Pulse rate (beats/minute) rhythm	Regular/ irregular		

Respiratory rate (breaths/ minute)		Per abdomen Bowel sounds	 Present/ Absent
Blood Pressure (mm Hg)		CNS(if abnormal specify) Sensorium(GCS) Motor Sensory Bladder Cerebellar Extra pyramidal Abnormal movents	 Normal/ Abnormal Normal/ Abnormal Normal/ Abnormal Normal/ Abnormal Normal/ Abnormal Present(specify)/ Absent
Temperature (degree Fahrenheit)		ECG(if abnormal specify) rate rhythm Intervals(PR,QT) segments(QRS, ST)	

		Waves(P,T,U)	
General examination Pallor skin turgor	 Yes/ No Normal/Abnormal	Any other atypical finding	

HB/TC/DC/Patelets		Urine Ca/Urine Cl/ K+	
LFT		Urine osmolality/ serum osmolality	
Urea/Creatinine		Trans tubular potassium gradient	
ABG		TSH/A1c/Cortisol	
Na/K/Bicarbonate		Ultrasound abdomen	
Mg/Ca/PO4		Any other relevant test	

Urine K/ creatinine; Ratio			

Dose of Potassium Required	Duration	Route

FINAL DIAGNOSIS	
FINAL OUTCOME	Death/ Discharged

CONSENT FORM

Annexure 2

Informed Consent form to participate in a research study

Study Title: *"Prospective Observational study to determine the causes of hypokalemia in medical wards and its association with other comorbidities and death"*

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

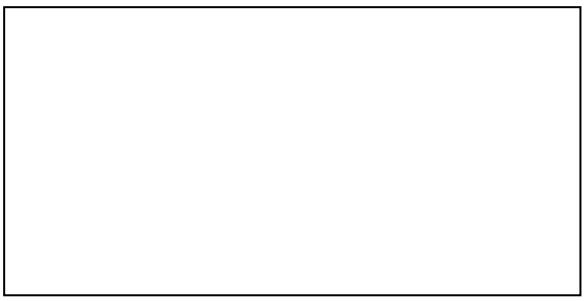
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or



Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

PATIENT INFORMATION SHEET

Annexure 3

CHRISTIAN MEDICAL COLLEGE, VELLORE

Department of General Medicine

TITLE: Prospective Observational study to determine the causes of hypokalemia in medical wards and its association with other comorbidities and death

INFORMATION SHEET

You are being requested to participate in a study to see the different causes of decreased potassium in the body. In this study, we will be seeing the factors that may affect this salt in our body which will include your age, gender and the place that you come from along with the various diseases that you already have in your body like high blood pressure or high blood sugars. Some other information like the medications you have been taking, any addicitions that you have and the reason as to what problem in your body brought you to the hospital will be asked. You will be examined physically for checking for the defect in any system in your body. We hope to include about 200 people from this hospital in this study.

Will there be any additional tests done in this study? We will not be conducting any additional tests in this study. All tests that are necessary to be done will be done by the concerned unit that you are admitted under.

Are there any side effects? Since we will only be observing the disease process in your body and we will not be giving you any additional medication, as a part of the study, there are no side effects.

If you take part what will you have to do? If you agree to participate in this study, you will be asked the details about the disease in your body and you will be examined physically for checking for the presence of any problem in your body. This information along with your test findings will be asked till the time that you are admitted in the hospital.

Can you withdraw from this study after it starts? Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury? We do not expect any injury to happen to you because of the study as we are only observing the disease that has afftected you and we will not be asking you to take any new medications apart from the ones prescribed by thr unit under whom you are admitted.

Will you have to pay any amount for the study? For being in the study, you do not have to pay any amount. You will have to pay only what your concerned unit under whom you have been admitted charges for your hospital stay and treatment and nothing extra to that amount.

What happens after the study is over? Once the study is over, we will look through the data that has been obtained to see how this salt(potassium) is affected in our body. With the information obtained we may be able to find new causes as well as develop newer tools for management of the condition.

Will your personal details be kept confidential? The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr.Roshni (telephone/mobile no.: 0416 2282039/ 9566571708), email: med3@cmcvellore.ac.in