TITLE:

A COMPARATIVE STUDY OF DIFFERENT MODALITIES USED IN THE EMERGENCY TREATMENT OF HYPERKALAEMIA IN PATIENTS WITH RENAL FAILURE AT THE KENYATTA NATIONAL HOSPITAL.

A DISSERTATION PRESENTED IN PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE (INTERNAL MEDICINE) OF THE UNIVERSITY OF NAIROBI.

BY

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DEDICATION

To my parents *Laban* and *Josephine Karanja* who have always been a source of much support and encouragement.

DECLARATION

I certify that this is my original work and has not been presented for a degree in any other University.

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ABBREVIATIONS

E.g.	-	For example
KNH	-	Kenyatta National Hospital
Ins	-	Insulin
Glu	-	Glucose
S. bicar	-	Sodium bicarbonate
Sal	-	Salbutamol
mmol/L	-	millimoles per litre
μmmol/L	-	micromoles per litre
iv	-	intravenous
g	-	grams
ECG	-	Electrocardiogram
%	-	percent
mls	-	millilitres
No.	-	Number
i.e.	-	that is

ACKNOWLEDGEMENTS

I wish to extend my sincere gratitude and appreciation to the following:-

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ABSTRACT

70 patients with acute renal (10 patients) and chronic renal (60 patients) failure with hyperkalaemia were managed at the Kenyatta National Hospital (KNH) medical wards and Renal Unit between August 1995 and January 1996. The patients were divided into 7 different treatment groups, each consisting of 10 patients. Treatment A group had glucose 25g i.v. with insulin 10 units i.v., Treatment B group had 50 mmol 8.4% Sodium bicarbonate infusion, Treatment C group had 0.5 mg salbutamol i.v. in 50 mls 5% Dextrose, Treatment D group a combination of treatments A and B, Treatment E group had a combination of treatments B and C, Treatment F group had a combination of treatments A and C, Treatment G group had a combination of treatments A and B and C.

Serum potassium was measured, 30 minutes, 1 hour, 2 hours, 4 hours and 8 hours after treatment. Plasma glucose concentration was measured before treatment and at 1 hour after in all patients. Electrocardiography was done before treatment on all patients and repeat ECG was done 30 minutes and 1 hour after treatment for the patients with features of hyperkalaemia on the initial ECG.

All the treatment modalities had satisfactory potassium lowering effect. The single treatment modalities A, B and C had a decrease in mean serum potassium at 1 hour of 1.14 ± 0.66 mmol/L ($p < 0.001$), 0.57 ± 0.22 mmol/L ($p < 0.001$) and 1.03 ± 0.41 mmol/L ($p < 0.001$) respectively. Results of treatments A and C were comparable. Treatment B induced the smallest decrease in potassium at 1 hour and also at all the other time intervals. Amongst the

2 treatment modalities combinations D, E, F the decrease in mean serum potassium at 1 hour was 1.18 $\pm$ 0.50 mmol/L ($p < 0.001$), 0.82 $\pm$ 0.40 mmol/L ($p < 0.001$) and 1.39 $\pm$ 0.66 mmol/L ($p < 0.001$) respectively. Treatment E induced the smallest decrease in potassium at 1 hour and also at all the other time intervals of the 2 treatment modalities combinations. Treatment E induced a lower decrease in mean serum potassium at all the time intervals compared to treatment C. Treatments D and F induced greater decreases in mean serum potassium at all time intervals when compared to the single treatment modalities. Treatment G had the greatest decrease in mean serum potassium at 1 hour of 1.54 $\pm$ 0.59 mmol/L ($p < 0.001$) and at all the other different time intervals when compared to the other treatment modalities.

Treatment A induced a significant decrease ($p < 0.05$) in the repeat plasma glucose concentration. 20% of the patients managed on treatment A had hypoglycaemia. Treatment B did not cause a significant decrease ($p = 0.648$) in the repeat plasma glucose concentration. Treatments C, E, F and G induced a significant increase ($P < 0.01$) in the repeat plasma glucose concentrations. Treatment D included a significant decrease ($p < 0.05$) in the repeat plasma glucose concentration, but no patient had hypoglycaemia.

The ECG features of hyperkalaemia did not correlate well with the serum potassium levels. The main changes on the features of hyperkalaemia on ECG occurred within the first 30 minutes after treatment.

Insulin with glucose and salbutamol were equally efficacious in lowering serum potassium in hyperkalaemia. The effect of the 2 treatment modalities combined was synergistic and seemed to protect against insulin induced hypoglycaemia. Combination of all 3 treatment modalities had the most efficacious result and seemed to prevent against insulin induced hypoglycaemia as well. The combination of salbutamol and sodium bicarbonate was not synergistic.

INTRODUCTION AND LITERATURE REVIEW

Potassium is a major intracellular cation, ninety-eight per cent of the total body potassium is located intracellularly at a concentration of 150 mmol/L. The extracellular concentration normally ranges from 3.5 - 5.0 mmol/L. Hyperkalaemia is defined as a serum potassium concentration greater than 5.0 mmol/L (1).

Hyperkalaemia develops whenever the rate of potassium intake or the rate of potassium efflux from cellular to extracellular fluid exceeds the sum of renal plus extra-renal potassium loses (2).

Hyperkalaemia is one of the commonest electrolyte abnormalities in acute or chronic renal failure (2). Acute renal failure is characterized by a rapid decline in renal function that leads to the accumulation of water, nitrogenous metabolites and crystalloid solutes in the body (3). Hyperkalaemia occurs early in acute renal failure due to the inadequate excretion of potassium (3). Metabolic acidosis which occurs in renal failure due to inadequate excretion of hydrogen ions worsens the hyperkalaemia by enhancing movement of potassium ions out of the cells (2). Chronic renal failure is characterized by progressive and irreversible decline in the glomerular filtration rate (3). Patients with progressive renal failure are able to maintain normal serum potassium levels until the final stages of uremia, due to the adaptations in the renal tubules and colonic sites where aldosterone and other factors serve to enhance potassium secretion. Hyperkalaemia then occurs when the glomerular filtration rate has reached levels of less than 5 ml/min. Hyperkalaemia in chronic renal failure can occur at a higher glomerular filtration

rate, when precipitated by metabolic acidosis, infections, blood transfusions, surgery, trauma or increased dietary potassium intake (4).

Hyperkalaemia causes changes in the electrical properties of cell membranes which results in neuromuscular and cardiac manifestations. The neuromuscular complaints are more common where the patients present with paraesthesias and weakness, progressing sometimes to ascending paralysis. The cardiac conduction abnormalities may lead to cardiac standstill (3).

The complications that may occur due to hyperkalaemia, make it necessary to lower the potassium levels urgently. The treatment of hyperkalaemia depends on the degree of the potassium elevation, the etiology, the presence or absence of symptoms and electrocardiographic findings (5). Hyperkalaemia is classified as mild, moderate or severe (1). The corresponding serum potassium levels for the various degrees of severity are as follows:-

Mild - serum potassium concentration of 5.0 - 6.5 mmol/L.

Moderate - Serum potassium concentration of 6.5 - 8.0 mmol/L.

Severe - serum potassium concentration of more than 8.0 mmol/L (1).

The management of hyperkalaemia involves using different treatment modalities, viz;

(i) Alteration of the transcellular gradient (shifting potassium from the extracellular fluid to the intracellular fluid).

(a) Glucose with Insulin

(b) Sodium bicarbonate

(c) Beta receptor agonists

(ii) Removal of potassium from the body

(a) Diuretics

(b) Cation exchange resins (Sodium polystyrene sulfonate)

(c) Dialysis (Peritoneal or haemodialysis)

iii) Reversal of membrane abnormalities

(a) Calcium gluconate

(b) Hypertonic sodium chloride.

(1)

The emergency treatment of hyperkalaemia in renal failure involves the use of treatment modalities that will cause alterations of the transcellular gradient. Calcium gluconate is also used when the serum potassium level is high, causing cardiac conduction abnormalities or neuromuscular symptoms. Calcium diminishes the depolarisation of the skeletal muscles produced by the hyperkalaemia, but has no effect on the serum potassium concentration (1).

Various studies have been carried out to find out the efficacy of the three main treatment modalities viz; glucose with insulin, sodium bicarbonate and beta receptor agonists used in the emergency treatment of hyperkalaemia in renal failure (6-13). These studies have shown that all the three treatment modalities are useful in lowering the potassium concentration in hyperkalaemia.

Insulin stimulates both glucose and potassium uptake by the cells. A number of studies have shown that the use of insulin with glucose in the treatment of hyperkalaemia may be associated

with hypoglycemia (6-8). The study by Allon and Copkney reported that the hypoglycemic effect of insulin is attenuated when co-administered with albuterol (8).

Metabolic acidosis which occurs in renal failure, causes hyperkalaemia by promoting the transfer of potassium out of the cells into the extracellular fluid. The management of metabolic acidosis with sodium bicarbonate helps in correcting the hyperkalaemia by reversing the movement of the potassium (1). Fraley and Alder, showed that sodium bicarbonate was useful in lowering the potassium level in hyperkalaemia, despite a constant pH (9).

Beta receptor agonists have been found to be useful in correcting the potassium level in hyperkalaemia (7,8,10-13). Beta receptor agonists stimulate the activity of the (Na^+ - K^+) ATPase, via stimulation of the cyclic adenosine monophosphate (8). The cell membrane bound (Na+ - K+) ATPase actively transports potassium into the cells counter balancing the passive leak of potassium from cells into the extracellular fluid (2). The beta receptor agonists may be useful both in the nebulized form and in the intravenous form (7,8,10-13). Comparative studies have been carried out to assess the efficacy and safety of the nebulized and intravenous forms of beta receptor agonists in treating hyperkalaemia (10-12). The studies demonstrated that both forms of the beta receptor agonists resulted in prompt and significant decrease in the serum potassium concentration. They were both simple, effective and safe methods to use. The intravenous form was found to act faster in lowering the serum potassium concentration.

Some studies have been carried out to compare the efficacy of two different treatment modalities, separately and in combination, Allon and Copkney, Fraley and Alder compared the efficacy of using insulin with glucose and a beta receptor agonist in lowering the serum potassium levels (8,9). The studies showed that both treatment modalities were efficacious in lowering the potassium concentration. The combination of both modalities was found to be more efficacious than either alone, and was safe. Insulin with glucose and a beta agonist in combination have an additive effect. Allon and Copkey in their study showed that intravenous insulin with glucose produced a significant decrease in serum potassium concentration within 15 minutes of drug administration and persisted for at least one hour (8). The maximal decrease occurred at about 45 minutes. Nebulized albuterol resulted in a significant decrease in the serum potassium concentration within 30 minutes and persisted thereafter for more than an hour. The maximal decrease occurred at about 60 minutes. The combination of intravenous insulin with glucose and nebulized albuterol produced the most marked decrease in serum potassium concentration. A significant decrease occurred within 15 minutes, a maximal decrease at about one hour and the significant decrease persisted for more than an hour.

One of the complications of hyperkalaemia is cardiac conduction abnormalities. The earliest manifestation of hyperkalaemia on the electrocardiogram is the peaking of the T-wave, which may appear when the serum potassium concentration exceeds 5.5 mmol/L. When the serum potassium level exceeds 6.5 mmol/L the QRS complex becomes widened. The QRS complex widens progressively with a rising concentration of serum potassium. When the serum potassium level is above 7.5 mmol/L intra-atrial and atrioventricular conduction are slowed,

the duration of the P-wave increases, it's amplitude diminishes and the P-R interval is prolonged. As the serum potassium is further increased, the P wave disappears, indicating abolition of atrial excitation and the QRS and it's S portion are greatly widened. The S-T segment may become elevated, though it may rarely be depressed. At serum potassium concentration of 12 mmol/L or at even lower levels, arrhythmias including asystole, ventricular fibrillation, aberrant junctional rhythms, escape rhythms and atrioventricular block occur (14).

FIGURE 1: ECG Features of hyperkalaemia

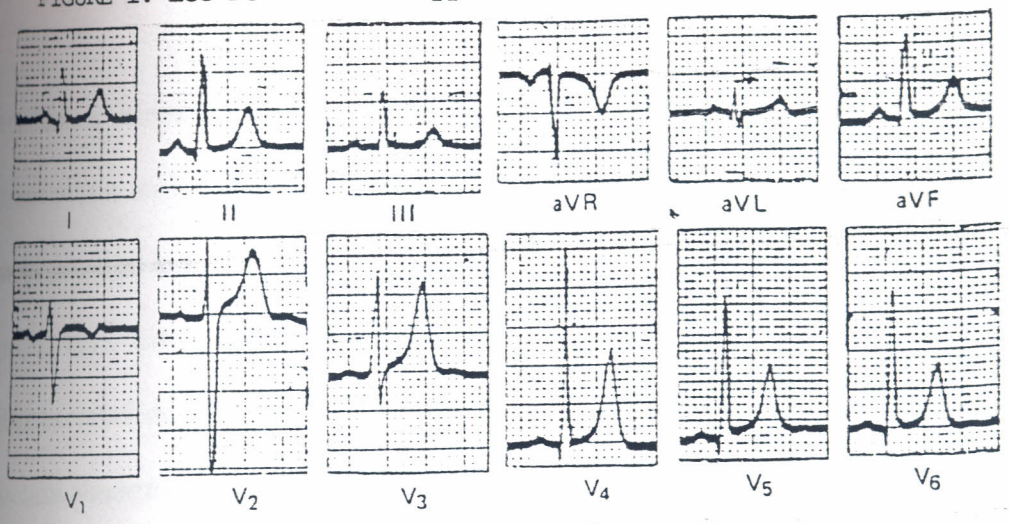


Figure 1 shows ECG features of hyperkalaemia. Tall T-waves seen in leads I, II, aVF and V_2- V_6 . Serum potassium level was 6.1 mmol/L. (15)

FIGURE 2: ECG Features of hyperkalaemia

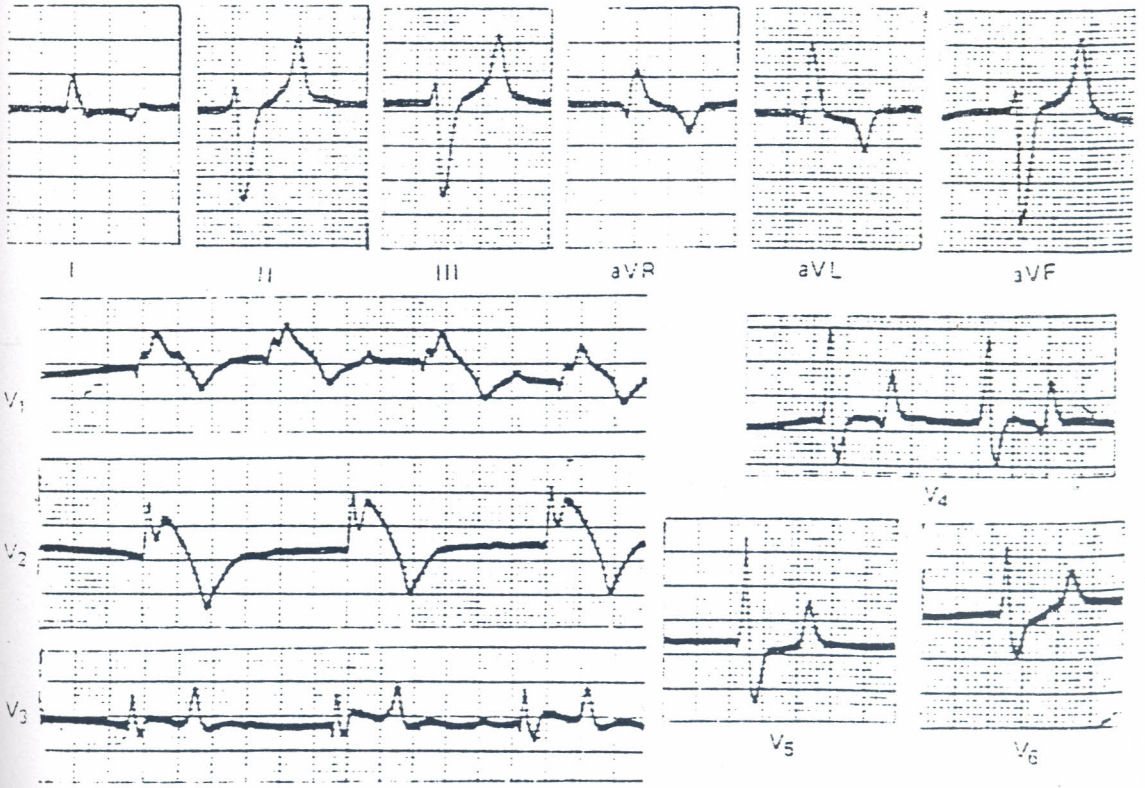


Figure 2 shows ECG features of hyperkalaemia occassional P-waves are seen. The rhythm is an incomplete AV dissociation. The QRS interval is widened to 0.14 s. The T waves are tall and peaked in II, III, aVF and V_3-V_6. Marked ST elevation in V_1 and V_3 serum potassium level was 9.3 mmol/L. (15)

Hyperkalaemia causes a reduction in the resting membrane potential. The giving of calcium gluconate causes an increase in the extracellular calcium concentration reducing the membrane threshold potential and restores normal membrane excitability. The effect of calcium gluconate is transient since it does not change the elevated serum potassium concentration, and the calcium is either excreted or taken up by bone. Calcium Gluconate can be repeated if life threatening conduction abnormalities or severe neuro-muscular symptoms still persist (5).

STUDY JUSTIFICATION

Hyperkalaemia is a common complication amongst patients with renal failure seen at the KNH. In most cases insulin with glucose has been used more or less exclusively over the years. No study has been carried out locally to determine efficacy and safety of the three different treatment modalities (insulin with glucose, sodium bicarbonate and beta receptor agonists) alone or in combinations, in the emergency treatment of hyperkalaemia in renal failure patients.

There is need to know the effectiveness of each treatment modality i.e. onset of action, maximum effect and the duration of effectiveness, so as to guide the local doctor on what to expect when managing hyperkalaemia.

The initiation of dialysis in patients with acute or chronic renal failure, in KHN tends to be delayed. This makes it important to start the patient with hyperkalaemia on the emergency treatment while awaiting dialysis. Emergency treatment of hyperkalaemia is important also in patients on conservative management of renal failure.

In the Renal unit at KNH, it has been found that patients with moderate to severe hyperkalaemia complain of general weakness, chest pain and tend to go into cardiac arrest when put on the haemodialysis machine before correcting the hyperkalaemia and giving calcium Gluconate [J.K. Kayima - Personal Communication].

Studies carried out in other countries, on the emergency treatment of hyperkalaemia in patients with renal failure using either sodium bicarbonate, insulin with glucose, a beta agonist (salbutamol), have found these different treatment modalities to be efficacious(5-8). Combination treatment of insulin with glucose and salbutamol has been found to be more efficacious than using either treatment modality alone.

STUDY OBJECTIVES

(i) To compare the efficacy of the three different treatment modalities, alone or in combinations, in the treatment of hyperkalaemia at different time intervals. Noting the time of maximal effect and the duration of activity for each of the treatment modality used, which included:-

(A) Insulin and glucose

(B) Sodium bicarbonate

(C) Salbutamol

(D) Sodium bicarbonate and insulin with glucose

(E) Sodium bicarbonate and salbutamol

(F) Salbutamol and insulin with Glucose

(G) Salbutamol and insulin with glucose and sodium bicarbonate.

ii) To assess the effect of the different treatment modalities on the blood sugar.

iii) To assess the effect of the different treatment modalities on patients with cardiac conduction abnormalities due to hyperkalaemia on the initial electrocardiogram.

MATERIALS

(a) Study area

The study was carried out in the adult Medical Wards and the Renal Unit at the Kenyatta National Hospital.

(b) Study population

Adult male and female patients with acute or chronic renal failure with hyperkalaemia.

(c) Drugs used for treatment

i) 50% Dextrose

ii) 8.4% Sodium bicarbonate

iii) Intravenous salbutamol.

(d) Laboratory equipment

i) Sterile needles and syringes

ii) Glucostrix strips

iii) Ames glucometer II

iv) Ciba coning 654 1SE $Na^+/K^+/Li^+$ analyzer

v) Technicon RA - 1000 machine for serum creatinine and urea

vi) Twelve Lead Siemes-Elema AB ECG machine

METHODOLOGY

(a) Study design.

This was a prospective single blind randomized study.

(b) Study size

70 patients were recruited into the study. This number was derived using the formula shown in Appendix I. (16)

(c) Case definition and selection

Inclusion criteria

i) Age above 13 years

ii) Patients with acute or chronic renal failure

iii) Serum potassium concentration greater than 5.0 mmol/L.

Exclusion criteria

i) Patients on beta receptor antagonists or beta receptor agonists

ii) Patients with hyperkalaemia following blood transfusion

iii) Patients with a history of exogenous intake of excessive potassium.

(d) Recruitment of patients

Patients who participated in the study were recruited using the consecutive sampling method, once they had fulfilled the selection criteria. The recruitment of the patients was done daily between 8 a.m. and 4 p.m. in the Medical wards and the Renal unit. The restricted randomization method was used in allocating the treatment modality to each patient, using the random permuted blocks.

i) Patients data - Including name, age and sex, were obtained by directly questioning the patient.

ii) Treatment modalities used in the study:-

(A) 50 mls of 50% Dextrose and 10 units of soluble insulin given intravenously over 15 minutes.

(B) 50 mmol of 8.4% sodium bicarbonate given intravenously over 15 minutes.

(C) Infusion of 0.5 mg salbutamol in 50 mls of 5% Dextrose given over 15 minutes.

(D) Combination of treatment (A) and (B)

(E) Combination of treatment (B) and (C)

(F) Combination of treatment (A) and (C)

(G) Combination of treatment (A) and (B) and (C).

(e) Laboratory tests

i) All blood for tests was obtained from a large vein in the ante cubital (no tourniquet) using a sterile needle and a sterile heparinised plastic syringe. The following laboratory tests were carried out:-

- Serum sodium and potassium levels were analysed using the method by Mass AHJ et al [17]. This method is based on ion selective electrode potentiometry which measures potentiometric change as function of ion concentration, automated through the ciba coning 654 1SE $Na^+/K^+/L1^+$ analyzer in the Renal unit.

- Serum creatinine was analyzed using the Technicon RA-1000 machine in the Renal unit, that uses the optimized Rossignol B et al [18] method. This method is based on the reaction of saturated picric acid with creatinine in an alkaline medium.

- Blood urea and Nitrogen was analyzed using the Technicon RA-1000 machine. The modified Tiffany TO et al [19] method was used. This method is based on the reduction of NADH to NAD which is directly proportional to the amount of urea in the blood sample.

- Random blood sugar was assessed using the Glucostix reagent strips and the Ames glucometer II. The method used in analysing the blood sugar is based on the glucose - oxidase coupled reaction [20].

ii) A twelve lead electrocardiogram was performed using the standard bipolar leads (leads I, II and III), the augmented extremity leads (aVR, aVF, aVL) and the unipolar precordial (chest) leads (V_1, V_2, V_3, V_4, V_5, V_6)as outlined by Goldman M.J. (15). The ECG machine used, was the Siemes-Elema AB (from the Department of Medicine, University of Nairobi).

The above investigations (i) and (ii) were carried out immediately before any treatment was given for the hyperkalaemia in all the selected patients.

iii) After treatment, repeat serial blood samples of 2 mls each were obtained to measure the serum potassium concentration. These serial samples were taken at

intervals of 30 minutes, 1 hour, 2 hours, 4 hours and 8 hours and anaysed immediately.

iv) Repeat electrocardiograms were performed after half an hour and one hour of treatment with any of the seven different treatment modalities. They were carried out on any patient found to have cardiac conduction abnormalities on the initial electrocardiogram.

(v) Repeat random blood sugar was carried out, using 1 ml of blood obtained, one hour after treatment with the different modalities in all patients.

(vi) Treatment with Calcium Gluconate

Patients found to a have serum potassium concentration of more than 7 mmol/L with or without electrocardiographic changes more severe than tenting of the T-wave, were given 10 mls of 10% calcium gluconate intravenously over 10 minutes.

(f) Data analysis

Patient's results were recorded on a study proforma (Appendix II).

Statistical analysis

i) **Analysis of the serum potassium levels**

The results were expressed in terms of range, mean + stand deviation for each

of the treatment modality used. The statistical significance of the differences between the seven treatment modalities used, was assessed by :-

(a) Finding the difference between the pre-treatment and post treatment potassium levels at different time intervals and using the multiple range test (Scheff's method) and the non-parametric ANOVA test.

(b) Using the repeated analysis of variance for the overall change.

ii) **Analysis of the plasma glucose concentrations**

The results were expressed in terms of range, mean + standard deviation for each of the treatment modality used. The statistical significance of the differences between the pre-treatment and post-treatment blood sugar for each of the seven treatment modalities was assessed using the one way analysis of variance, the non-parametric (Wilcoxon matched pairs signed rank test) and the parametric test *(paired sample t-test)*.

iii) Analysis of the Electrocardiograms

The changes in the repeat electrocardiograms taken half an hour and one hour after treatment for hyperkalaemia were assessed.

The data was analysed using SPSS/PC+ computer analysis programme.

(g) Ethical considerations

Informed verbal consent was sought from the patients before being included in the study. It was made clear to the patients that the drugs to be used were safe.

A written consent was granted by the Kenyatta National Hospital research and ethical committee, prior to the study being carried out.

FIGURE 3: DISTRIBUTION OF THE SERUM UREA LEVELS OF PATIENTS WITH HYPERKALAEMIA STUDIED

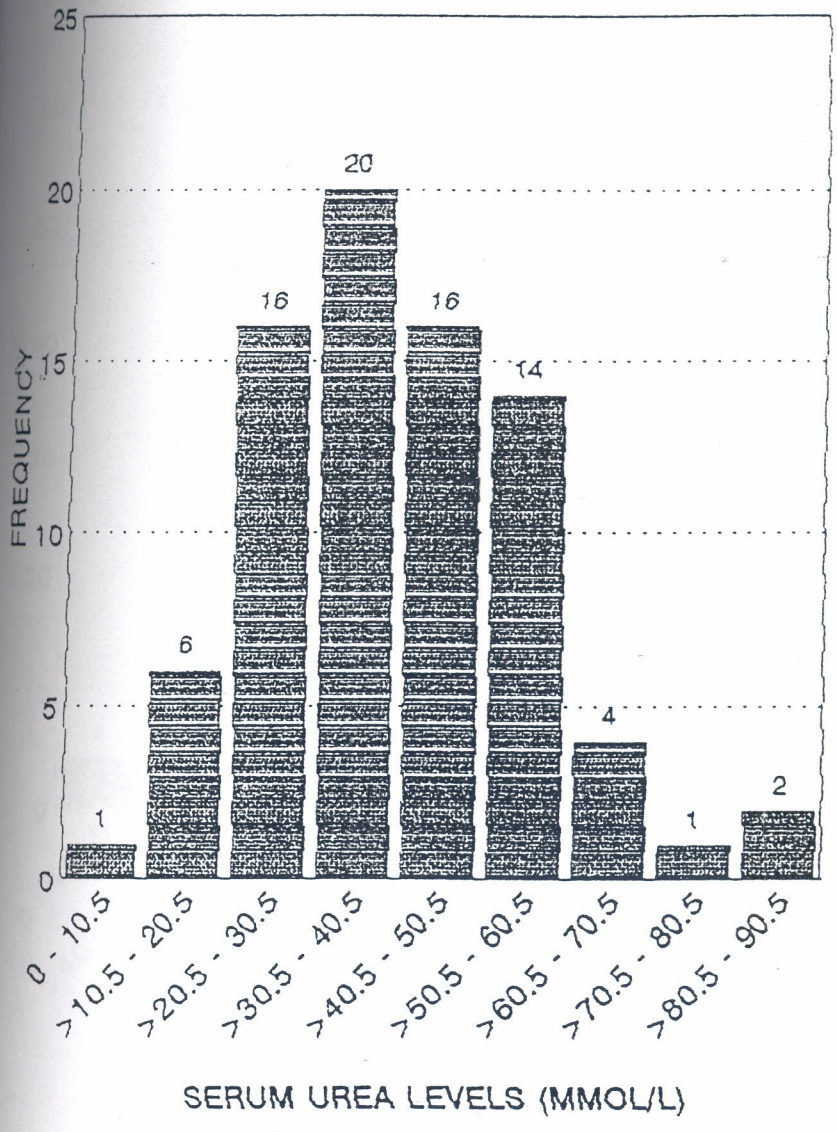


Figure 3 shows the distribution of the serum urea levels of patients with hyperkalaemia studied. The serum urea levels ranged from 9.60-83.70 mmol/L, with mean ± S.D. of 37.72 ± 14.84 mmol/L. There was no statistically significant difference in the serum urea ($p = 0.336$) between the different treatment groups.

FIGURE 4: DISTRIBUTION OF THE SERUM CREATININE LEVELS OF PATIENTS WITH HYPERKALAEMIA STUDIED

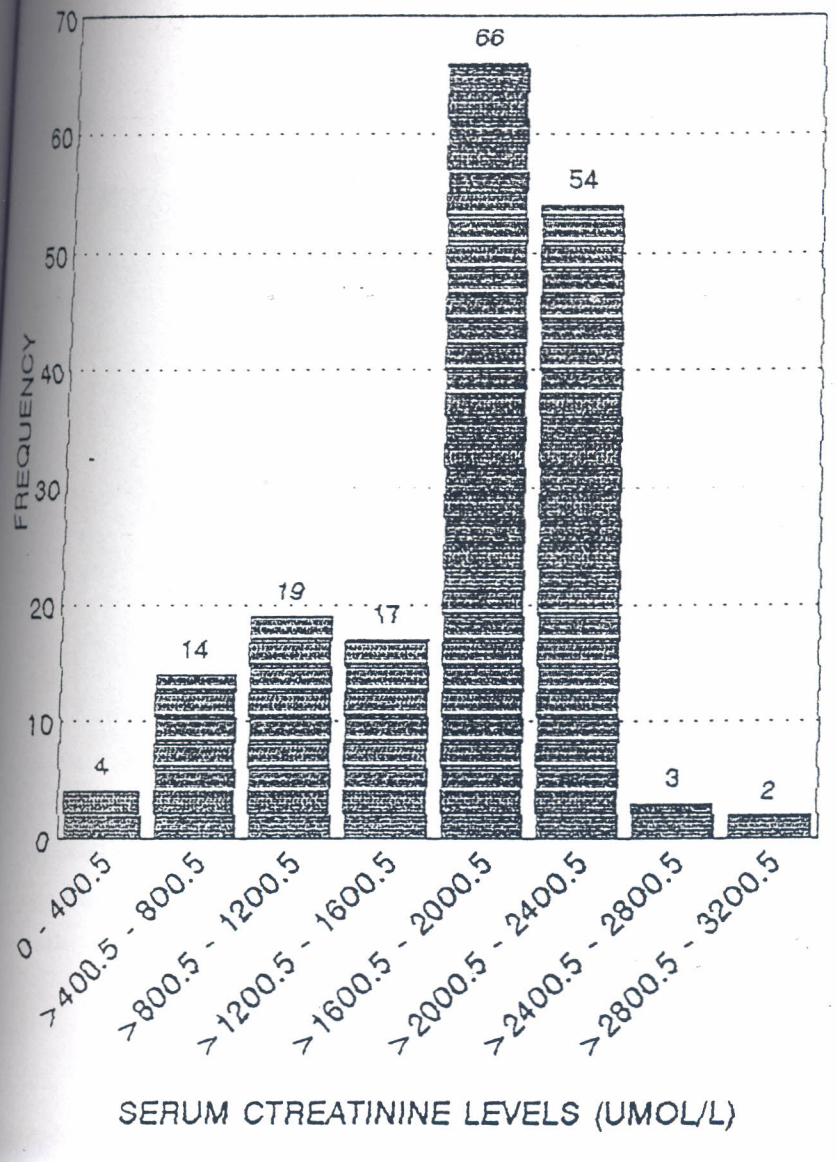
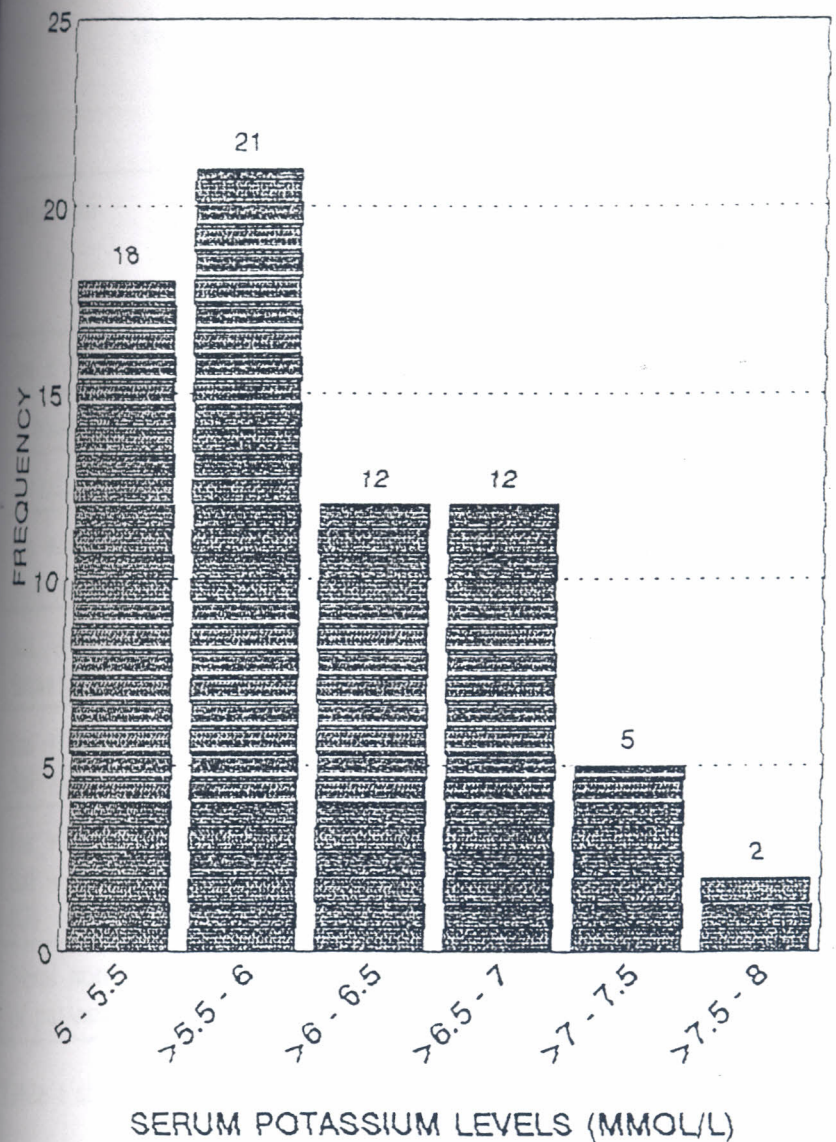


Figure 4 shows the distribution of the serum creatinine levels of the patients with hyperkalaemia studied.

The serum creatinine levels ranged from 174.0-3046.0 μmmol/L, with a mean ± S.D. 124 2.87 μmmol/L. There was no statistically significant difference in the serum creatinine (p = 0.234) between the different treatment groups.

FIGURE 5: DISTRIBUTION OF THE INITIAL SERUM POTASSIUM LEVELS OF THE PATIENTS WITH HYPERKALAEMIA STUDIED



gure 5 shows the distribution of the initial serum potassium vels of the patients with hyperkalaemia studied. The serum tassium ranged from 5.10 - 7.89 mmol/L with a mean ± S.D. of 6.04 .70 mmol/L . There was statistically significant difference in serum potassium (p = 0.015) between the different treatment ups.

Table 1: Number of patients in the different treatment groups at different time intervals, after initiating the various treatment modalities for hyperkalaemia.

Treatment	Number of patients					
	Initial	30 minutes	1 hour	2 hours	4 hours	8 hours
Ins + Glu (A)	10	10	10	10	10	9
S. bicar (B)	10	10	10	10	10	10
Sal (C)	10	10	10	10	10	9
Ins + Glu + S. bicar (D)	10	10	10	10	8	8
Sal. + S. Bicar (E)	10	10	10	10	10	9
Ins + Glu + Sal. (F)	10	10	10	10	10	9
Ins + Glu + Sal + S. bicar (G)	10	10	10	10	10	9
Total number of patients	70	70	70	70	68	63

Table 1 shows the number of patients in the different treatment groups at different time intervals, after initiating the various treatment modalities for hyperkalaemia.

Of the 70 patients seen at the beginning of the study, 63 (90%) completed the 8 hour study period. By 4 hours of the study period, 2 patients (2.9%) had been started on dialysis. By 8 hours of the study period, 5 other patients (7.1%) had been started on dialysis. 2 patients started on dialysis died during the 8 hour study period. All the 7 patients were started on dialysis

because of severe uraemia. Their serum potassium levels ranged from 5.03-7.68 mmol/L with a mean $\pm$ S.D. of 6.14 $\pm$ 0.95 mmol/L. The two patients who died had serum potassium levels of 5.31 mmol/L and 5.81 mmol/L before dialysis.

10 mls of 10% Calcium Gluconate was given intravenously to 9 patients (12.9%) in whom the serum potassium was more than 7 mmol/L. Of these 6, patients had acute renal failure.

FIGURE 6: DISTRIBUTION OF MEAN DIFFERENCE IN SERUM POTASSIUM LEVELS BETWEEN INITIAL AND SPECIFIED TIME AFTER TREATMENT BY TREATMENT MODALITY

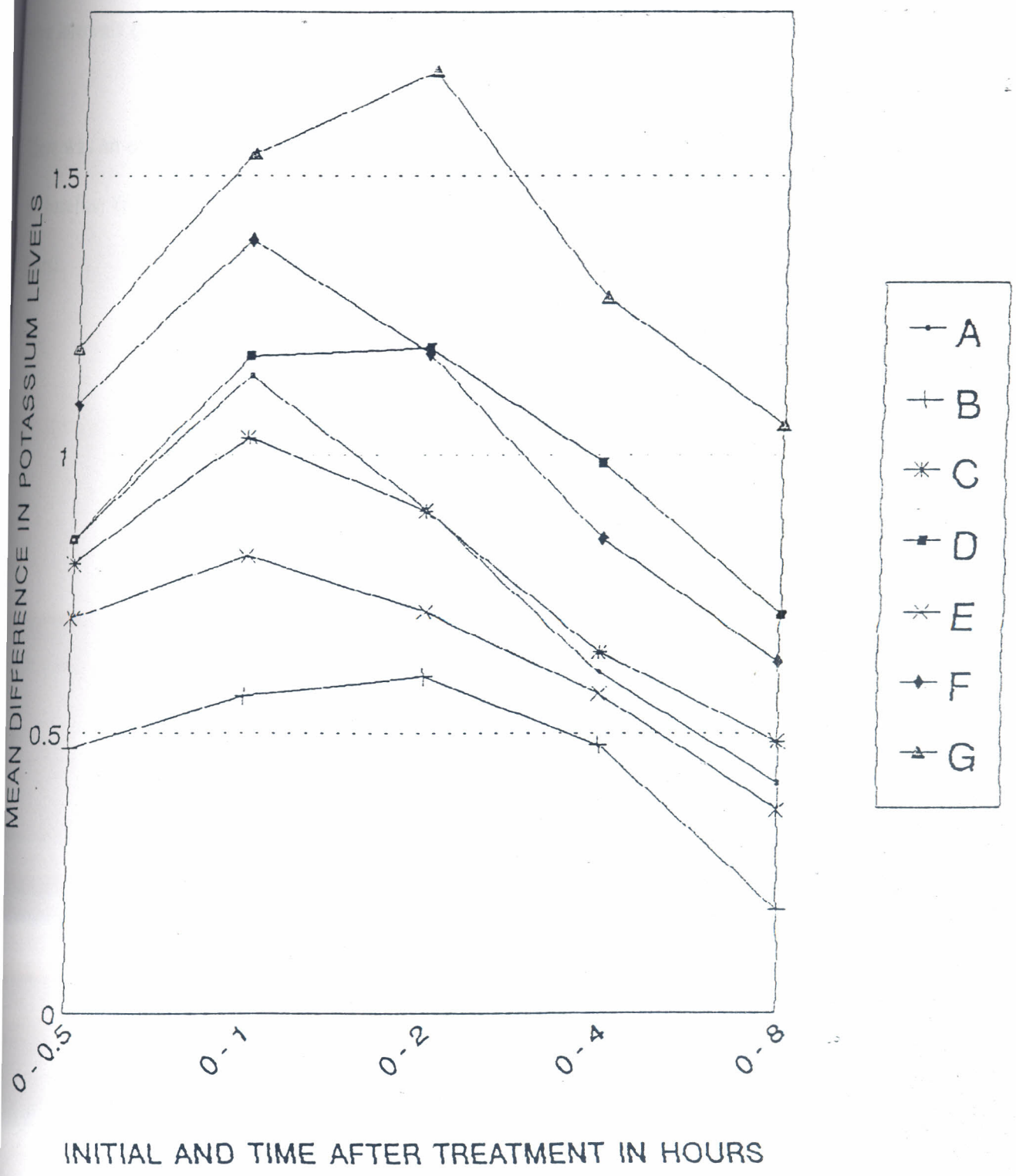


Figure 6 shows the mean serum potassium levels of the different treatment modalities at different time intervals. There is an overall similar change (rapid decrease in the serum potassium level with a gradual rise), in all the treatment modalities. The maximal decrease occurred at 1 to 2 hours in the different treatment modalities.

There was no statistically significant difference between the treatment modalities at the different time intervals ($p = 0.794$).

There was an overall statistically significant change ($p < 0.01$)in serum potassium levels from the baseline (time O) to the different time intervals (30 minutes, 1 hour, 2 hours, 4 hours, 8 hours).

FIGURE 7: DISTRIBUTION OF MEAN SERUM POTASSIUM LEVELS BY TREATMENT MODALITY FOR THE FIRST 2 HOURS OF THE STUDY PERIOD

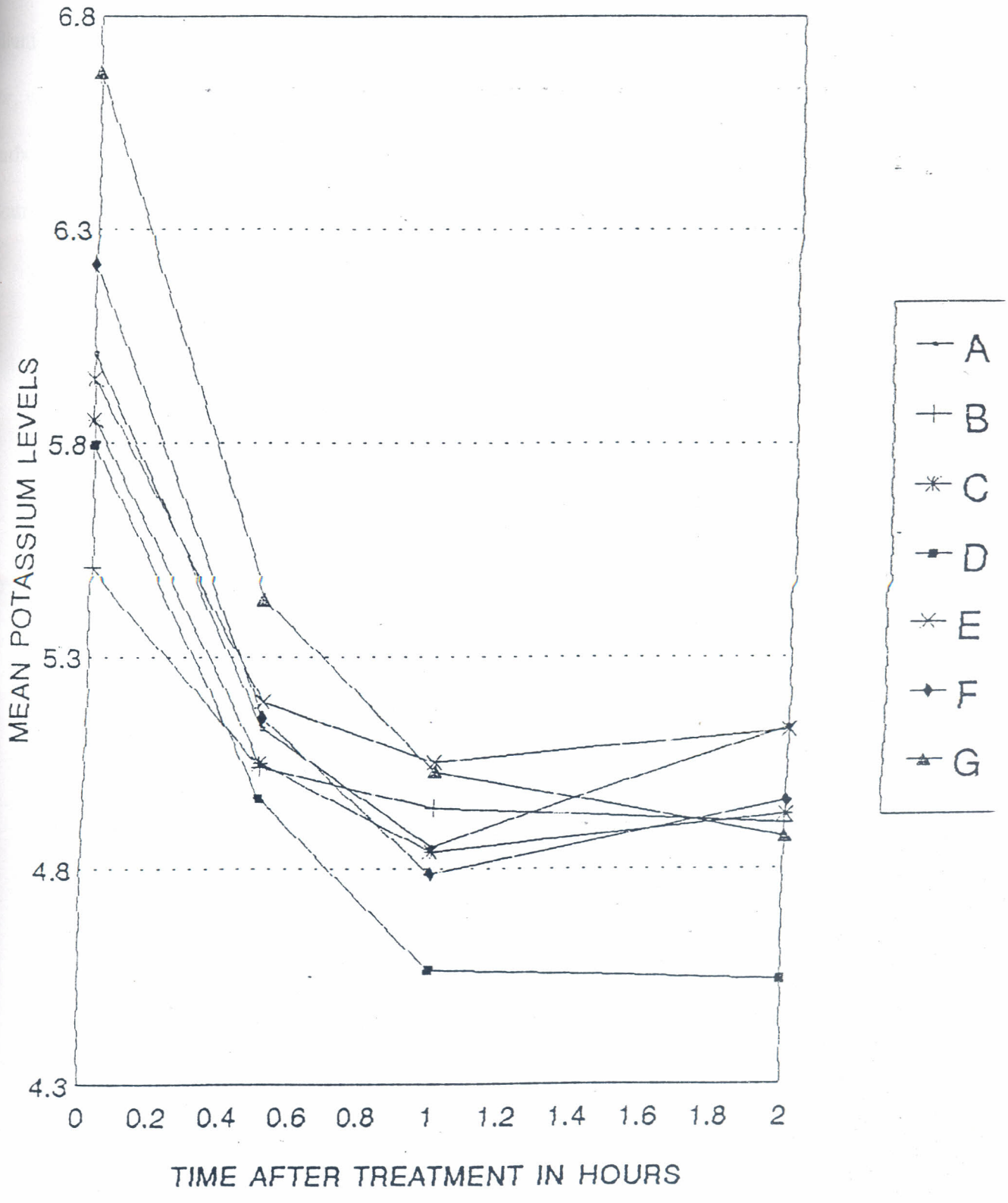


Figure 7 shows the mean serum potassium of the different treatment modalities within the first 2 hours of the study period. In all the treatment modalities there was a rapid onset of action and a significant decrease in the serum potassium within the first 30 minutes.

The maximal decrease in mean serum potassium for insulin with glucose (A), salbutamol (C), sodium bicarbonate and salbutamol (E), insulin with glucose and salbutamol (F) occurred at 1 hour, while the maximal decrease with sodium bicarbonate (B), insulin with glucose and sodium bicarbonate (D), insulin with glucose and salbutamol and sodium bicarbonate (G) occurred at 2 hours.

GURE 8: DISTRIBUTION OF MEAN SERUM POTASSIUM LEVELS BY TREATMENT MODALITY FOR THE 8 HOUR PERIOD

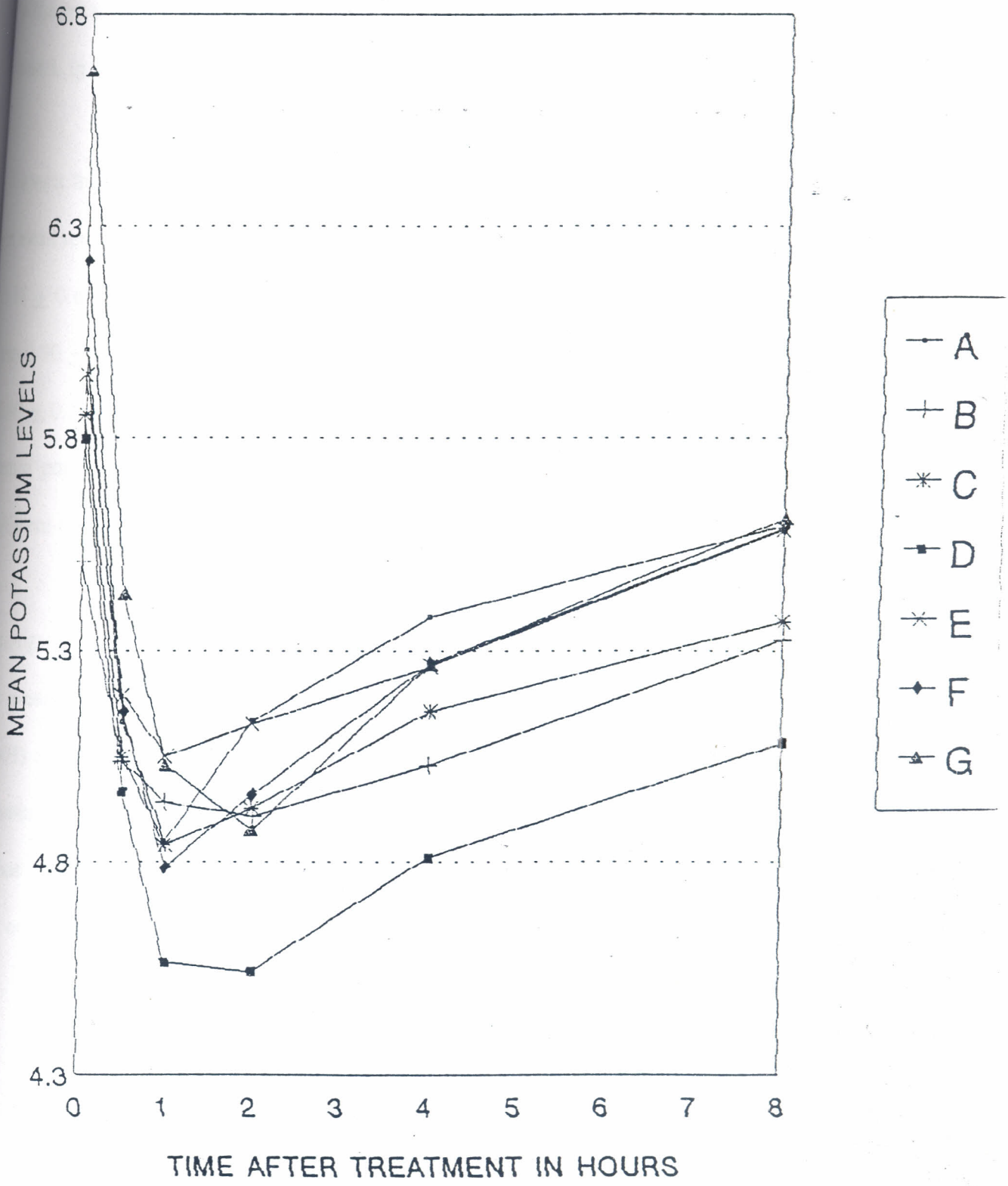


Figure 8 shows the mean difference in the serum potassium level between the initial and the various time intervals after treatment, for the different treatment modalities. The greatest decrease in mean serum potassium at all the different time intervals occurred with the combination of the three treatment modalities consisting of insulin with glucose, salbutamol and sodium bicarbonate (G). The maximal decrease occurred at 2 hours and was 1.69 $\pm$ 0.54 mmol/L ($p < 0.001$).

Amongst the single treatment modalities, insulin with glucose (A) caused the greatest decrease in mean serum potassium at 30 minutes of 0.85 $\pm$ 0.47 mmol/L ($p < 0.001$) and at 1 hour of 1.14 $\pm$ 0.66 mmol/L $p < 0.001$). At 2 hours the decrease caused by insulin with glucose (A) was 0.90 $\pm$ 0.45 mmol/L ($p < 0.001$) which was comparable to that caused by salbutamol (C) 0.90 $\pm$ 0.56 $\pm$ mmol/L ($p < 0.001$). Sodium bicarbonate (B) had the lowest decrease in mean serum potassium at 30 minutes of 0.47 $\pm$ 0.31 mmol/L ($p = 0.001$) and at all the other different time intervals.

Amongst the 2 treatment modality combinations, insulin with glucose and salbutamol (F) caused the greatest decrease in mean serum potassium at 30 minutes of 1.09 $\pm$ 0.58 mmol/L ($p < 0.001$) and at 1 hour of 1.39 $\pm$ 0.66 mmol/L ($p < 0.001$). At 2 hours the decrease caused by salbutamol and insulin with glucose (F) of 1.18 $\pm$ 0.69 mmol/L ($p < 0.001$) was comparable to that of insulin with glucose and sodium bicarbonate (D) of 1.19 $\pm$ 0.50 mmol/L ($p = 0.002$). The combination of sodium bicarbonate and salbutamol (E) had the lowest decrease in mean

serum potassium at 30 minutes of 0.71 $\pm$ 0.43 mmol/L ($p = 0.001$) and at all the other different time intervals.

The decrease in serum potassium using salbutamol and insulin with glucose (F) was greater than that using either treatment modality alone. The combination of insulin with glucose and sodium bicarbonate (D) also gave a greater decrease in serum potassium than when using either treatment modality alone. The decrease in serum potassium using salbutamol and sodium bicarbonate (E) was greater than when using sodium bicarbonate (B) alone but was less than when using salbutamol alone (C).

There was a significant statistical difference between the initial serum potassium and the serum potassium at the different time intervals for all the treatment regimens ($p < 0.01$), except with sodium bicarbonate (B) where the difference between the initial serum potassium and the serum potassium at 8 hours was not statistically significant ($p=0.181$). The difference was statistically significant at the other time intervals ($p < 0.01$) with sodium bicarbonate (B).

The number of patients tested for both the initial and repeat plasma glucose concentration 1 hour after treatment was 70. The range for the initial plasma glucose concentration was 2.70 - 19.40 mmol/L with a mean $\pm$ S.D. of 6.27 $\pm$ 2.98 mmol/L and a median of 5.4 mmol/L. The range for the repeat plasma glucose concentration 1 hour after treatment was 2.70 - 19.40 mmol/L with a mean $\pm$ S.D. of 6.94 $\pm$ 3.15 mmol/L and a median of 6.55 mmol/L.

The difference in the mean plasma glucose concentration between the initial and repeat plasma glucose for the whole study population was -0.67 $\pm$ 1.71 mmol/L which was statistically significant ($p = 0.001$).

Table 2: The difference between the initial and repeat mean plasma glucose concentration in the different treatment modalities.

Treatment	Initial mean plasma glucose concentration (mmol/L)	Repeat mean plasma glucose concentration (mmol/L)	Difference in mean plasma glucose concentration (mmol/L)
Ins + Glu.(A)	6.79 $\pm$ 2.42	5.00 $\pm$ .04	+ 1.79 $\pm$ 0.80
S. bicar (B)	6.06 $\pm$ 1.43	6.13 $\pm$ 1.45	-0.07 $\pm$ 0.47
Sal (C)	5.29 $\pm$ 2.07	6.84 $\pm$ 2.27	-1.55 $\pm$ 1.37
Ins + Glu + S. bicar. (D)	6.48 $\pm$ 3.46	5.89 $\pm$ 3.24	+0.59 $\pm$ 0.74
Sal + S. Bicar. (E)	7.64 $\pm$ 3.91	9.68 $\pm$ 4.25	-2.04 $\pm$ 1.10
Ins + Glu + Sal (F)	5.12 $\pm$ 1.23	7.42 $\pm$ 1.65	-2.0 $\pm$ 1.38
Ins + Glu + Sal + S. bicar (G)	6.50 $\pm$ 4.68	7.64 $\pm$ 4.27	-1.14 $\pm$ 0.93

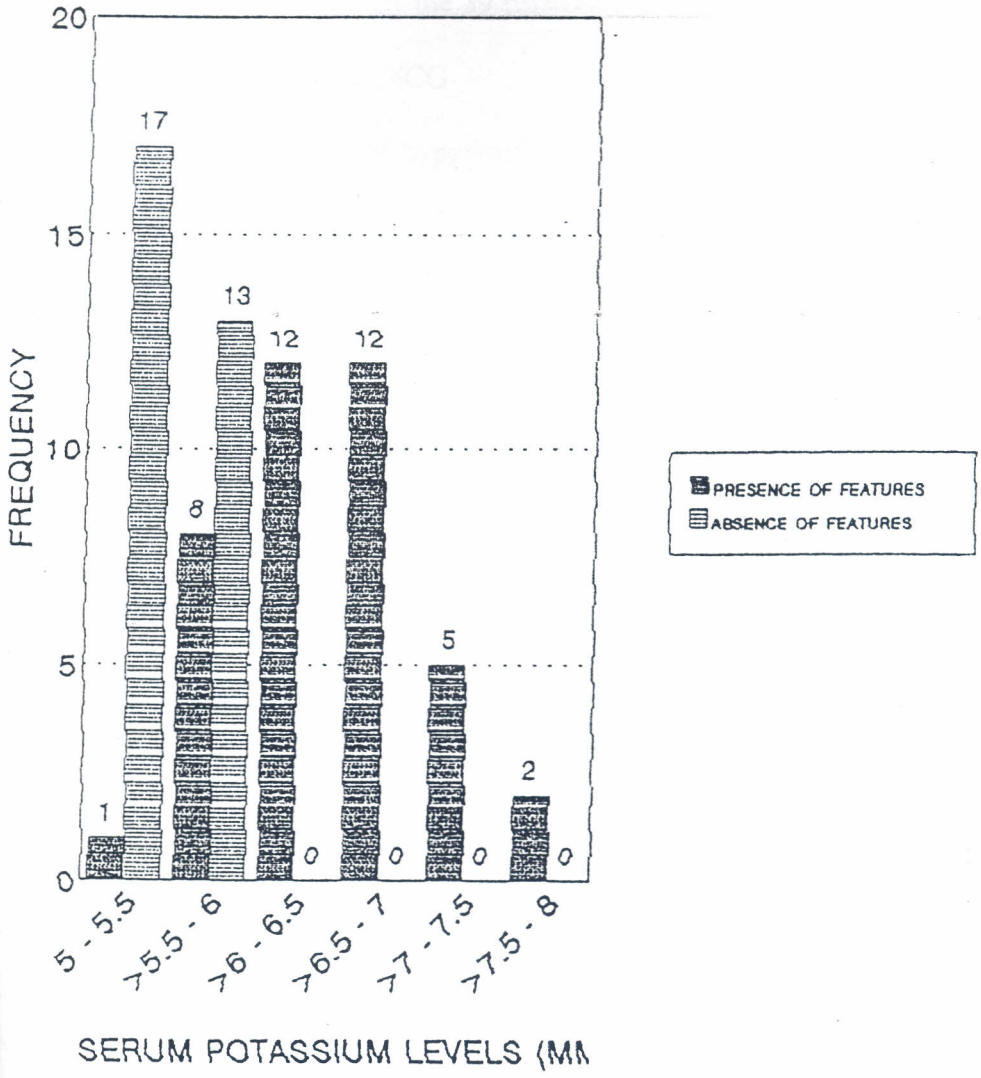
Table 2 shows the difference between the initial and repeat mean plasma glucose concentration in the different treatment modalities.

The slight increase in the repeat plasma glucose concentration of 0.07 $\pm$ 0.47 mmol/L with sodium bicarbonate (B) was not statistically significant ($p = 0.648$).

The increase in repeat plasma glucose concentration using salbutamol (C), salbutamol and insulin with glucose (F), salbutamol and sodium bicarbonate (E), salbutamol and insulin with glucose and sodium bicarbonate (G) were all statistically significant ($p < 0.01$).

The decrease in repeat plasma glucose using insulin with glucose (A) alone, insulin with glucose and sodium bicarbonate (D) are both statistically significant ($p < 0.05$).

FIGURE 9: DISTRIBUTION OF THE NUMBER OF ECG'S WITH OR WITHOUT FEATURES OF HYPERKALAEMIA AT DIFFERENT SERUM POTASSIUM LEVELS



igure 9 shows the distribution of number of ECG's with or without atures of hyperkalaemia at different serum potassium levels

30 patients (42.9%) had normal initial ECG. The potassium range of these 30 patients was 5.10-5.99 mmol/L. All the 31 patients with a serum potassium above 6.0 mmol/L had features of hyperkalaemia on ECG. Of the 39 patients with serum potassium levels $\leq$ 6.0 mmol/L, 30 patients (77%) had a normal ECG.

Table 3: The features of hyperkalaemia on the initial ECG in the 70 patients seen in the study.

ECG features of hyperkalaemia	Number of patients	Percentage
None (normal ECG)	30	42.9
Tall peaked T-waves	17	24.3
Tented T-waves (normal amplitude)	14	20.0
2 + Flattened, broad P-waves	1	1.4
13 + 9 + Depressed ST segment	1	1.4
10 + 9 + Depressed St segment	2	2.9
13 + Flattened, broad P-wave	1	1.4
16 + Depressed St segment	1	1.4
1 + prolonged PR interval	1	1.4
10 + prolonged QT interval	1	1.4
14 + Flattened, broad p-wave	1	1.4
Total Number	70	100.0

N.B.: Refer to Appendix III for the ECG Code Book.

Table 3 shows the features of hyperkalaemia on the initial ECG in the 70 patients seen in the stud 30 patients (42.9%) had normal ECG. 31 patients (44.3%) had only T-wave abnormality on ECG whom 14 (20%) had tented T-waves of normal amplitude and 17 (24.3%) had Tall-peaked T-wa 9 patients (12.8%) had ECG features more severe than T-wave abnormality only.

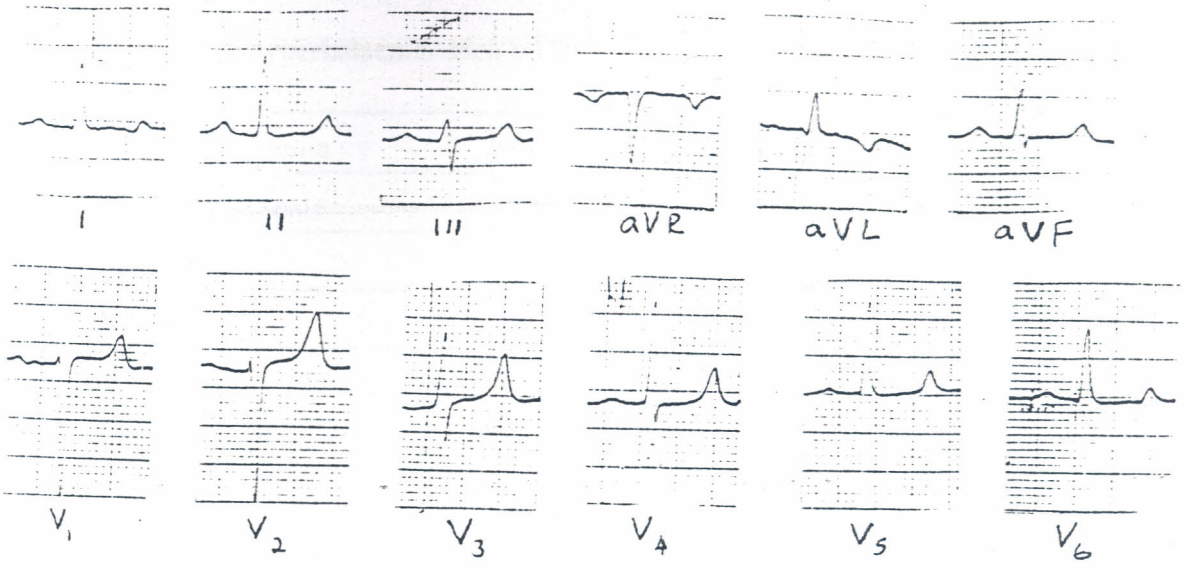


Figure 10 shows features of hyperkalaemia seen in the initial ECG of patient No. 69. Tented T-waves seen in leads II, III, aVF, V_5 and V_6. Prolonged P.R. and QT intervals, flattened and broad P-waves. The serum potassium level was 5.79 mmol/L.

FIGURE 11: Initial ECG features of patient No. 23

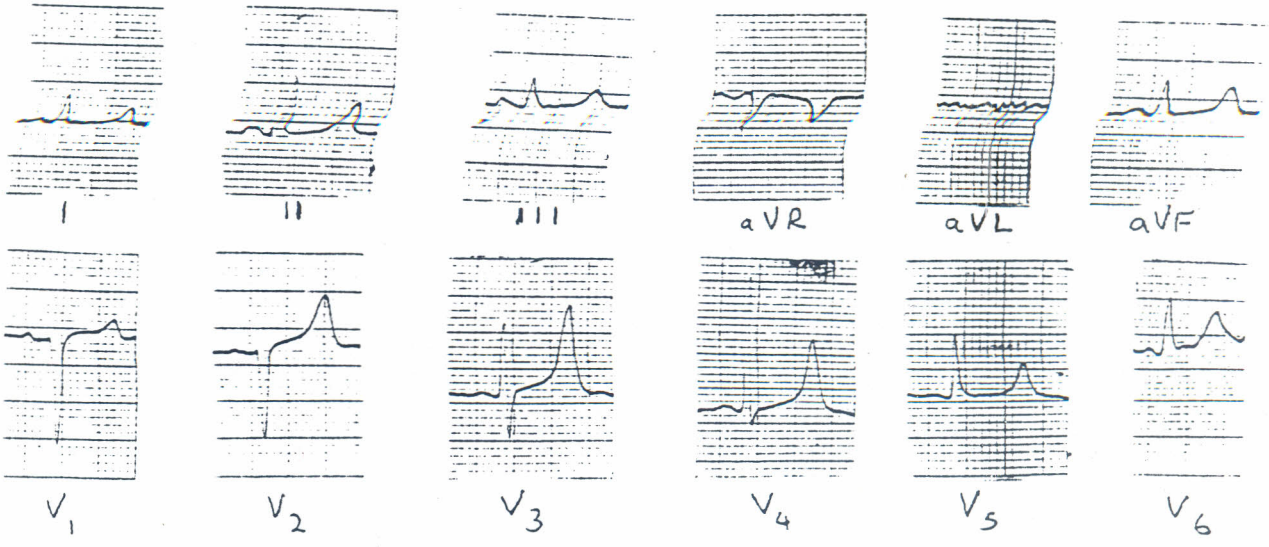


Figure 11 shows features of hyperkalaemia seen in the initial ECG of patient No. 23. Tall T-waves are seen in leads II, aVF, V_2 - V_6 . Prolonged QT interval, flattened P-waves. The serum potassium level was 6.22 mmol/L.

Table 4: Features of hyperkalaemia seen on the repeat ECG 30 minutes after treatment.

ECG features of hyperkalaemia	Number of patients	Percentage
Not done (initial ECG normal)	30	42.9
None (normal ECG)	20	28.6
Tall peaked T-waves	8	11.4
Tented T-waves (normal amplitude)	6	8.6
2 + widened QRS	1	1.4
9 + prolonged QT interval	1	1.4
2 + 7	1	1.4
2 + prolonged PR interval	1	1.4
10 + prolonged QT interval	1	1.4
1 + 9 + Depressed St segment	1	1.4
Total number	70	100.0

N.B.: Refer to Appendix III for the ECG Code Book.

Table 4 shows the features of hyperkalaemia seen on the repeat ECG 30 minutes after treatment.

The repeat ECG 30 minutes after treatment was done on 40 patients, who had features of hyperkalaemia on their initial ECG. Of these 40 patients, 20 patients (50%) had their electrocardiograms normalised 30 minutes after treatment. 14 patients (35%) had only T-wave abnormality on ECG, 6 of these patients (15%) had tented T-waves of normal amplitude, while 8 (20%) had tall peaked T-waves. 6 patients (15%) had ECG features more severe than T-wave abnormality.

FIGURE 12: Repeat ECG 30 minutes after treatment of hyperkalaemia in Patient No. 69.

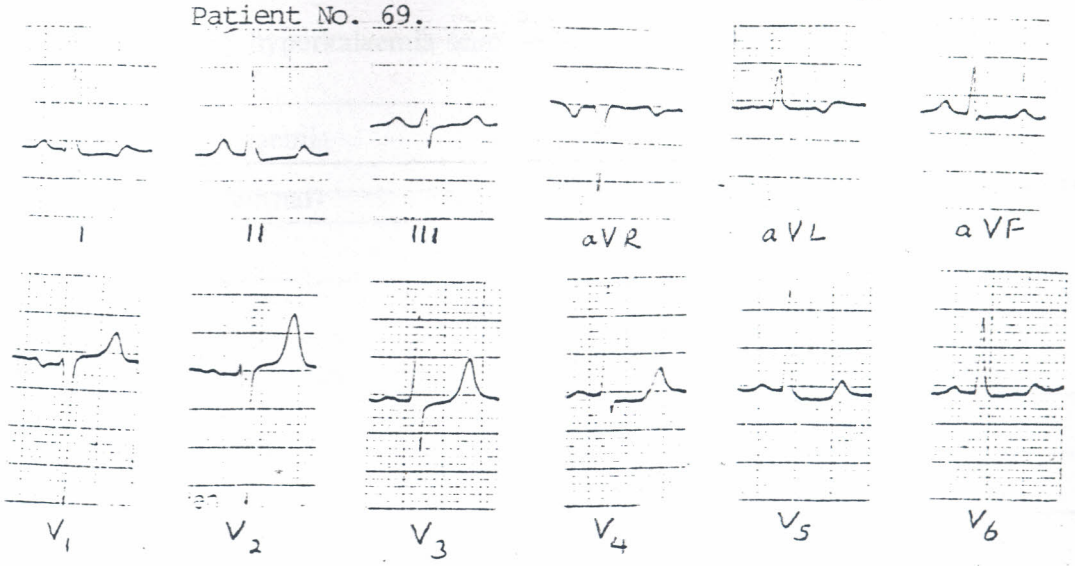


Figure 12 shows repeat ECG 30 minutes after treatment of the hyperkalaemia in patient No. 69. There are no features of hyperkalaemia. The serum potassium level was 4.24 mmol/L.

FIGURE 13: Repeat ECG 30 minutes after treatment of hyperkalaemia in patient No. 23

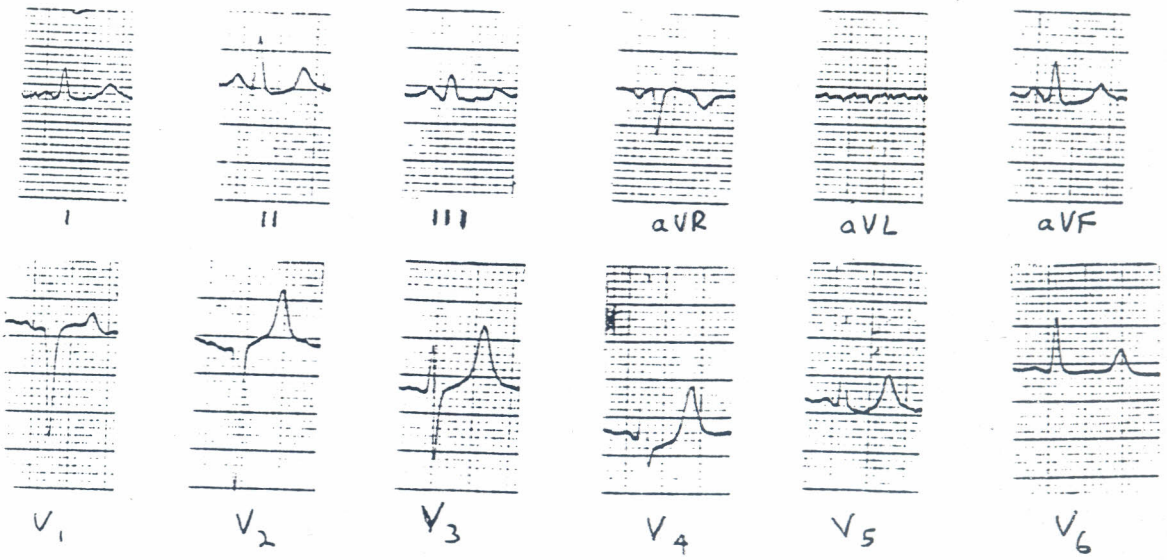


Figure 13 shows features of hyperkalaemia seen in the repeat ECG, 30 minutes after treatment of hyperkalaemia in patient No. 23. Tall T-waves seen in leads II, V_2 - V_5. The serum potassium level was 4.92 mmol/L.

Table 5: Features of hyperkalaemia seen on the repeat ECG 1 hour after treatment.

ECG features of hyperkalaemia	Number of patients	Percentage
Not done (initial ECG normal)	30	42.9
None (normal ECG)	21	30.0
Tall peaked T-waves	8	11.4
Tented T-waves (normal amplitude)	6	8.6
2 + widened QRS	1	1.4
Widened QRS	2	2.9
10+ prolonged QT interval	1	1.4
1 + 9 + Depressed St segment	1	1.4
Total Number	70	100.0

N.B.: Refer to Appendix III for the ECG Code Book.

Table 5 shows the features of hyperkalaemia seen on the repeat ECG 1 hour after treatment. The repeat ECG 1 hour after treatment was done on 40 patients, who had features of hyperkalaemia in their initial ECG. Of these 40 patients, 21 patients (52.5%) had their electrocardiogram normalised 1 hour after treatment. 14 patients (35%) had only T-wave abnormality on ECG. 6 of these patients (15%) had tented T-waves of normal amplitude while 8 patients (20%) had tall peaked T-waves. 5 patients (12.5%) had ECG features more severe than T-wave abnormality.

The main ECG changes occurred 30 minutes after treatment. There was not much difference between the ECG after 30 minutes and the one 1 hour after treatment.

Figure 14: Repeat ECG 1 hour after treatment of hyperkalaemia in patient No. 6

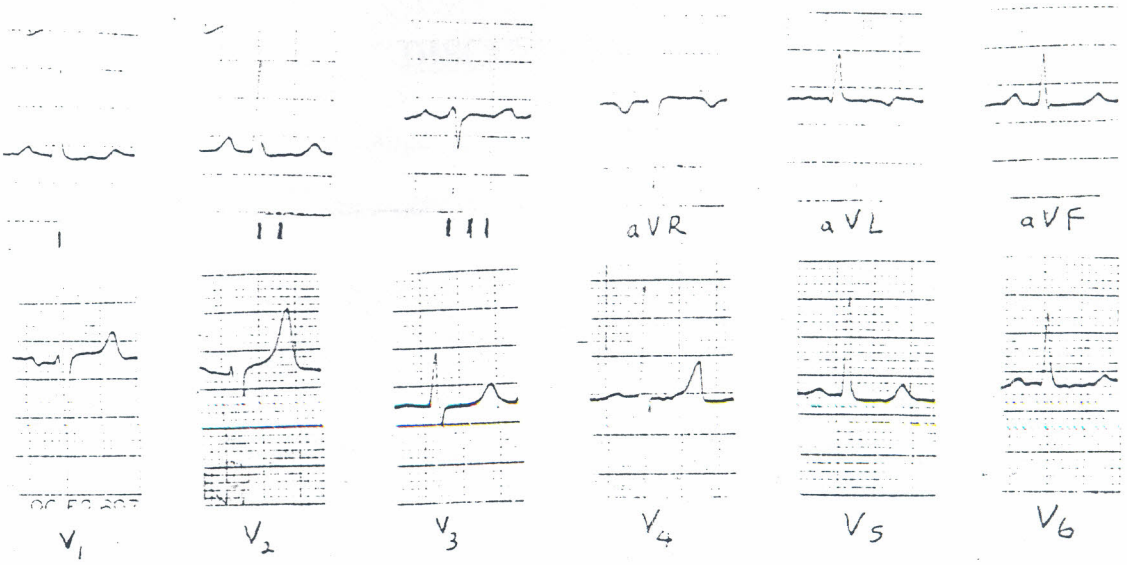


Figure 14 shows the repeat ECG 1 hour after treatment of the hyperkalaemia in patient No. 69. There are no features of hyperkalaemia. The serum potassium level was 4.30 mmol/L.

Figure 15: Repeat ECG 1 hour after treatment of hyperkalaemia in patient No. 23.

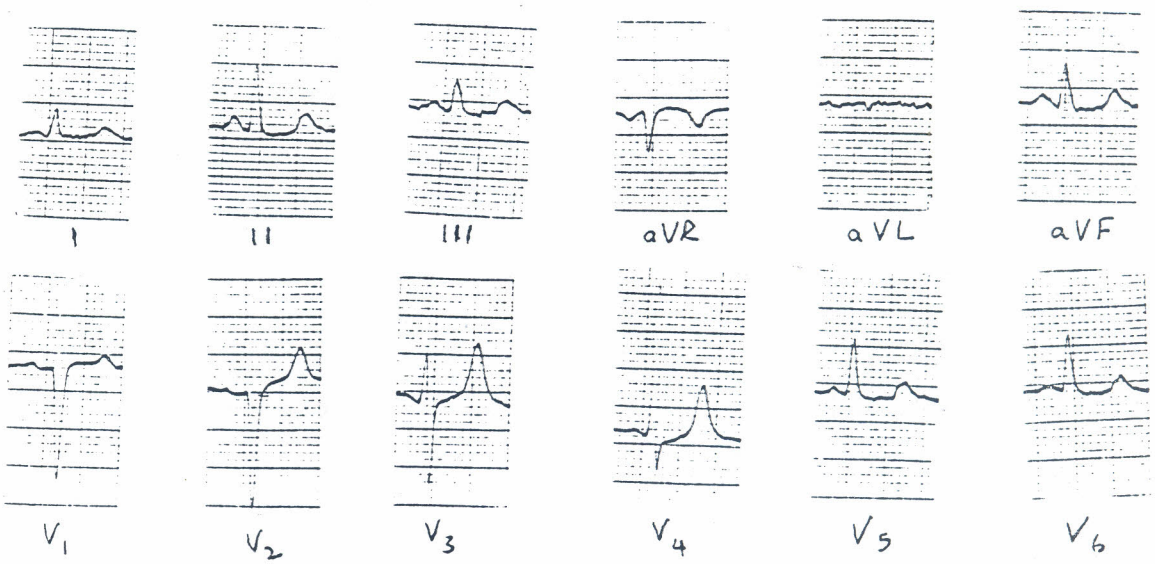


Figure 15 shows the repeat ECG 1 hour after treatment of hyperkalaemia in patient No. 23. There are no features of hyperkalaemia. The serum potassium level was 3.95 mmol/L.

DISCUSSION

Hyperkalaemia is a common and dangerous electrolyte abnormality, occurring in acute and chronic renal failure (2). In the emergency treatment of hyperkalaemia one aims at the reversal of the membrane abnormalities by the use of calcium gluconate and the restoration of the transcellular potassium gradient by the use of insulin with glucose and sodium bicarbonate which are the most commonly recommended treatment modalities (1). Insulin stimulates the activity of the Na^+ - K^+ pump enhancing the uptake of potassium into the cell (1). Sodium bicarbonate promotes the transfer of potassium into the cells irrespective of the acid-base status (9). Recently beta receptor agonists either singly or in combination with insulin and glucose have been found to be useful in the treatment of hyperkalaemia (8,10). Beta receptor agonists lower the serum potassium by stimulating the activity of (N^+ - K^+) ATPase via stimulation of the cyclic adenosine monophosphate, which results in the net shift of potassium from the extracellular to the intracellular compartment.

The age distribution in this study showed that most patients were young, a reflection of the age of patients with chronic renal failure at the KNH (J.K. Kayima - Personal Communication). The majority of the patients with hyperkalaemia studied (85.7%) had chronic renal failure.

The initial mean serum potassium showed statistical differences amongst the treatment modalities. This statistical differences did not affect the outcome of the results, since each treatment lowered the serum potassium level irrespective of the initial serum potassium level.

In this study, the maximal decrease in mean serum potassium at 1 hour using insulin (10 units) and glucose (25g) was 1.14 $\pm$ 0.66 mmol/L. This was higher than the decrease of 0.65 $\pm$ 0.09 mmol/L reported by Allon and Copkney, using similar quantities of insulin and glucose (8). The only difference being that they gave insulin as a bolus first before giving the glucose infusion. The giving of glucose infusion first, stimulates the release of insulin which together with the insulin bolus given later have an additive effect in stimulating the activity of the Na^+ - K^+ pump. Lens et al found a mean decrease of serum potassium of 1.5 $\pm$ 0.2 mmol/L at 1 hour which is comparable to the results of this study (7). They used 40g of glucose and 10 units of insulin.

In this study a maximal decrease in mean serum potassium of 1.03 $\pm$ 0.41 mmol/L at 1 hour using 0.5 mg intravenous salbutamol was comparable to the studies by Allon et al and lens et al (10,7). Allon, Copkney and Dunlay R found that using 20 mg of nebulized salbutamol caused a maximal decrease in mean serum potassium of 0.98 $\pm$ 0.14 mmol/L at 1 hour (10). Lens et al using 0.5 mg intravenous salbutamol found a maximal decrease in mean serum potassium of 1.0 $\pm$ 0.1 mmol/L at 1 hour (7).

Liou et al compared the use of intravenous salbutamol infusion and nebulized salbutamol in the management of hyperkalaemia in patients with renal failure and found that both routes of administration were equieffective in decreasing the serum potassium concentration, with minimal side effects (11,12).

A comparable significant decrease in mean serum potassium was seen in the 10 patients given sodium bicarbonate infusion in this study. The significant decrease occurred at all the time intervals when serum potassium level was measured, except for the 8 hour time interval. Sodium bicarbonate caused the smallest decrease in serum potassium when compared to the other treatment modalities used in this study. Blumberg et al found that sodium bicarbonate did not have a significant hypokalaemic effect in 10 haemodialysis patients seen (21). Fraley and Alder found there was a significant decrease in the serum potassium when sodium bicarbonate infusion was given to the 14 patients with hyperkalaemia, irrespective of their acid-base status (9).

In this study, the combined treatment with salbutamol and insulin with glucose gave a maximal decrease in mean serum potassium of 1.39 $\pm$ 0.66 mmol/L at 1 hour which is comparable to 1.21 $\pm$ 0.19 mmol/L found by Allon and Copkney (8).

Sodium bicarbonate in combination with insulin and glucose gave a greater decrease in the mean serum potassium than using either treatment modality alone. The decrease was not additive.

The decrease in mean serum potassium using sodium bicarbonate and salbutamol was less compared to using salbutamol alone, but greater compared to using sodium bicarbonate alone. The reason for the non-synergistic effect of sodium bicarbonate and salbutamol is not clear.

The combination of sodium bicarbonate, salbutamol and insulin with glucose gave a greater decrease in mean serum potassium at all the time intervals, compared to any of the 3 treatment

modalities used alone or any of the 2 treatment modality combinations. The effect of the 3 treatment modalities was not additive.

All the 7 different treatment modalities resulted in a significant decrease in the mean serum potassium during the 8 hour study period, except for sodium bicarbonate at the 8 hour interval where the decrease was not significant. In all the treatments, after achieving the maximal decrease at either 1 to 2 hours, there was a gradual rise in the serum potassium.

Insulin with glucose alone was found to cause a decrease in the repeat plasma glucose concentration at 1 hour in all the 10 patients seen. Hypoglycaemia occurred in 20% of the patients. Allon and Copkney reported that 75% of their patients given 10 units of insulin bolus followed by 25g of glucose infusion for 5 minutes had hypoglycaemia by 1 hour (8). The number of patients who developed hypoglycaemia was much higher, compared to the findings in this study where 25g of glucose infusion was given over 15 minutes followed by 10 units of insulin bolus. This shows that hypertonic glucose infusion should precede and not follow the insulin bolus in the management of hyperkalaemia to help reduce hypoglycaemic side effects. Ijutic and Rumboldt came up with the same recommendation in their study (22).

Salbutamol was found to cause a significant increase in the repeat plasma glucose concentration 1 hour after treatment in this study. This was comparable to the finding by Allon and Copkney (8). Salbutamol stimulates gluconeogenesis thus promoting hyperglycaemia(23).

Sodium bicarbonate did not have a significant effect on the repeat plasma glucose concentration 1 hour after treatment in both this study and that by Fraley and Alder (9).

Salbutamol in combination with insulin and glucose caused a significant increase in the repeat plasma glucose concentration 1 hour after treatment in this study. This was comparable to the finding by Allon and Copkney (8).

The combination of sodium bicarbonate and insulin with glucose caused a significant decrease in the repeat plasma glucose concentration, but it did not cause hypoglycaemia in any of the 10 patients seen.

Sodium bicarbonate and salbutamol in combination caused a significant increase in the repeat plasma glucose concentration.

The combination of sodium bicarbonate, salbutamol and insulin with glucose had a significant increase in the repeat plasma glucose concentration.

The main changes on the features of hyperkalaemia on the ECG occurred within 30 minutes of administering any of the treatment modality. There were no major differences in the changes on the repeat ECGs between the different treatment modalities. 24.3% of the initial ECGs had tall peaked T-waves. This was comparable to the finding by Baun H.A. et al, where 22% of the patients with hyperkalaemia had the characteristic Tall-peaked T-waves (24). Levine H.D.

et al found the tent-shaped symmetrical T-waves with a narrow base and normal amplitude to be the earliest or the sole electrocardiographic evidence of hyperkalaemia in some individuals(25). This finding was confirmed in this present study.

Hyperkalaemia produces changes in the electrocardiogram which become increasingly more severe as the potassium ion concentration rises. This correlation has been best demonstrated in animals with experimental hyperkalaemia but not in humans with spontaneous clinical hyperkalaemia and it is neither precise nor totally consistent (26,27). In this study there was no direct correlation between the degree of hyperkalaemia and ECG changes, making an ECG not a very useful tool in the diagnosis of the level of hyperkalaemia.

In a recent poll of 63 directors of nephrology training programmes, beta receptor agonists were never included in the treatment of hyperkalaemia in renal failure as an initial or two subsequent treatment modality. Insulin with glucose was the most frequently recommended treatment modality. Sodium bicarbonate was also recommended either singly or in combination with insulin and glucose (28).

The present study and those by Lens et al, Allon and Copkney, show salbutamol to be as effective as insulin with glucose in lowering serum potassium in hyperkalaemia. The three studies also show that the combination of salbutamol and insulin with glucose is more effective than with either treatment modality alone. This combination also prevents the insulin induced hypoglycaemia. In this study insulin with glucose and salbutamol is the most effective of the

2 treatment modality combinations. The combination of salbutamol, sodium bicarbonate and insulin with glucose was the most effective and prevented insulin-induced hypoglycaemia.

Beta receptor agonists used singly or in combination with other treatment modalities are useful in lowering the serum potassium. They can be given through the intravenous route or the nebulizer. The nebulized form is easy to give especially when there is no ready venous access. The nebulized and the intravenous form of beta receptor agonists have been found to have minimal effect on the blood pressure and pulse rate (10). In this study beta receptor agonists have been found to be as effective as reported in other studies.

CONCLUSIONS

1. Insulin with glucose, salbutamol and sodium bicarbonate when used singly or in combinations are useful in lowering the serum potassium in hyperkalaemia.
2. Insulin with glucose and salbutamol when used also are equally effective in lowering the serum potassium in hyperkalaemia.
3. The combination of insulin with glucose and salbutamol is the most effective of the 2 treatment modality combinations.
4. The combination of insulin with glucose and salbutamol and sodium bicarbonate is the most effective, compared to the single or 2 treatment modality combinations.
5. All the treatments achieve a rapid decrease in serum potassium within the first 30 minutes of treatment with maximal decrease at 1 to 2 hours and a gradual rise of serum potassium thereafter. The decrease in serum potassium was significant with all treatment modalities during the 8 hour study period except for treatment with sodium bicarbonate whereby the serum potassium had risen significantly by 8 hours of treatment.
6. Salbutamol causes a rise in plasma glucose. In combination with insulin and glucose, it prevents the insulin induced hypoglycaemia.
7. The electrocardiogram is not a very useful tool in determining the serum potassium level and in monitoring the level during treatment.

RECOMMENDATIONS

1. Intravenous salbutamol should be included in the management protocol of hyperkalaemia at the KNH since it is cheaper, easy to use, has minimal side effects and is as effective as insulin with glucose.
2. The use of combination therapy using insulin with glucose and salbutamol with or without sodium bicarbonate, insulin with glucose and sodium bicarbonate should be encouraged since they are more effective than single treatment modalities.
3. Insulin should only be given as a bolus after a hypertonic glucose infusion, and the blood sugar level should be measured 1 hour after treatment.
4. Further studies using sodium bicarbonate and salbutamol in combination should be carried out, to find whether the non-synergistic effect is an incidental finding or not.
5. A study involving the use of oral beta receptor agonists (eg. volmax) in the treatment of hyperkalaemia should be carried out, to determine if the oral route will have any hypokalaemic effect, the onset and duration of action and the presence of any side effects. The oral route if found to be as efficacious as the intravenous and inhalation routes, would be ideal since it would be easier to administer and it would cost less.

REFERENCES

1. KUNIS C.L. and LOWENSTEIN J.

   The emergency treatment of hyperkalaemia.

   Med. Clinic North Am. 1981; 65:165-176.

2. WYNGAARDEN J.B., SMITH L.H., BENNETT J.C. (Eds)

   Cecil Textbook of Medicine 19th Edition.

   W.B. Saunders Company; Philadelphia, 1992.

3. CAMERON S., DAVISON A.M., GRUNFELD J.P. KERR D. and RITZ E. (Eds).

   Oxford Textbook of Clinical Nephrology.

   Oxford University Press, New York, 1992.

4. WILSON J.D., BRAUNWALD E., ISSELBACHER K.J., PETERSDORF R.G., MARTIN J.B., FAUCI A.S., ROOT R.K. (Eds).

   Harrison's Principles of internal Medicine 12th Edition.

   Mc Graw - Hill Inc., New York, 1991.

5. Editorial - Hyperkalaemia - silent and deadly.

   The Lancet 1989; 1:1240.

6. SWILLIAMS P.S., DAVNPORT A., BONE J.M. Hypoglycemia following treatment of hyperkalaemia with insulin and dextrose (Abstract). Post grad. Med. J. 1988; 64:30-32.

7. LENS X.M., MONTOLIU J., CASES A., CAMPISTOL J.M., REVERT L. Treatment of hyperkalaemia in renal failure. Salbutamol vs insulin (Abstract). Nephrol Dial Transplant 1989; 4:228-232.

8. ALLON M. and COPKNEY C. Albuternol and insulin for treatment of hyperkalaemia in haemodialysis patients.
Kidney Int. 1990; 38:869-872.

9. FRALEY D.S. and ALDER S. Correction of hyperkalaemia by bicarbonate despite constant blood pH.
Kidney Int. 1977; 12:354-360.

10. ALLON M. DUNLAY R. and COPKNEY C. Nebulized albuterol for acute hyperkalaemia in patients haemodialysis.
Ann. Intern. Med. 1989;110:426-429.

11. LIOU H.H., CHIANG S.S., WU S.C., HUANG T.P. Intravenous infusion or nebulization of salbutamol for treatment of hyperkalaemia in patients with chronic renal failure (Abstract) Chung Hua I Hsueh Tsa Chih (Taipei).
(TAIWAN) 1994;53:276-281.

12. LIOU H.H., CHIANG S.S., WU S.S., HUANG T.P., CAMPESE V.M. and YANG W.C., SMOGORZEWSKI M.: Hypokalaemic effect of intravenous infusion or nebulization of salbutamol in patients with chronic renal failure: comparative study (Abstract) Am.J. Kidney Dis. 1994; 23: 266-271.

13. NEVILLE A., PALMER J.B.D., GADDIE J., MAY C.S., PLAMER K.N.V. and MURCHISON L.E. : Metabolic effects of salbutamol: Comparison of aerosol and intravenous administration. Br. Med. J., 1977; 1: 413-414.

14. FRIEDBURG C.K., Diseases of the heart.
3rd Edition. W.B. Sanders Company. Philadelphia, 1966.

15. GOLDMAN M.J.

Principles of clinical electrocardiography 12th Edition.

Los Altos, California, 1986.

16. Sample size determination - A User's Manual Epidemiological and Statistical Methodology Unit. W.H.O. Geneva, 1986.

17. MASS A.H.J., SIGGAARD-ANDERSEN O., WEISBERG H.F. and ZIJLSTRAWG.

Ion-selective electrodes for sodium and potassium.

Clin. Chem. 1985;31:482-485.

18. ROSSIGNOL B., ROSSIGNOL D. and PETIT CLERIC C.

Improvement of creatinine measurement on RA-1000.

Clin. Biochm. 1984; 17(3):203-204.

19. TIFFANY T.O., JANSEN J.M., BURTIS C.A., OVERTON J.B. and SCOTT C.D.

Enzymatic Kinetic rate and end point analyses of substrate by use of GEMSAEC fast analyzer.

Clin Chem 1972; 18:829.

20. KAPLAN L.A. and PESCE A.J.

Clincial chemistry. Theory analysis and correlation.

2nd Edition.

C.V. Mosby Company; St. Louis Missouri, 1989.

21. BLUMBERG A., WEIDMANN P., SHAW S., GNADINGER M.

Effects of various therapeutic approaches on plasma potassium and major regulating

factors in terminal renal failure [Abstract].

Am. J. Med. 1988; 85:507-512.

22. IJUTIC D. and RUMBOLDT Z. Should glucose be administered before, with or after insulin in the management of

hyperkalaemia (Abstract)

Renal Failure 1993; 15:73-76.

23. CLAUSEN T., EVERTS M.E. Regulation of Na^+ K^+ pump in skeletal muscle.

Kidney Int. 1989; 35: 1-13.

24. BAUN H.A., SURAWILZ B., BELLET S.

T waves in hyperpotassaemia.

A.M. J. Med. Sci. 1955; 230:147-150.

25. LEVINE H.D., JEHANGIR, P., VAZIFDAR J.P. Tent shaped T-waves of normal amplitude in potassium intoxication.

Am. Heart J., 1952; 43:437-450.

26. JULIAN D.G., WILSON P.A., CANIM A.J., FOX K.M. and HALL R.J.C. (Eds).

Diseases of the heart.

Baillierre Tindall Company, London, 1989.

27. HURST J.W., LOGUE R.B., RACKLEY C.E., SCHILANT R.C., SONNENBLICK E.H., WALLACE A.G., WENGER N.K. (Eds).

The heart, arteries and Veins.

Mc Graw-Hill Book Company, Newyork, 1982.

28. IQBAL Z., FRIEDMAN E.A.:

preferred therapy of hyperkalaemia in renal insufficiency: Survey of nephrology training - program directors (Letter).

N. Engl. J. Med. 1989; 32: 60-61.

APPENDIX I

Sample size Estimation

$$n = \frac{(z\alpha + Z\beta^{2})(6_1^2 + 6_2^2)^2}{(\mu_1 - \mu_2)^2}$$

n = minimum number of patients in each treatment option.

$z\alpha$ = significance

$z\beta$ = power of the test

6_1^2 = sample 1 variance or (S.D)

μ_1 = mean sample 1

μ_2 = mean of sample 2.

6_2^2 = sample 2 variance or $(S.D.)^2$

Using a level of significance of $p<0.05$, power of 90%, standard deviation of 0.3 and a difference between the means of 0.5 then

n = 8.

The minimum sample size is 54 patients.

vii) Repeat random blood sugar one hour after treatment of the hyperkalaemia.....

viii)Repeat electrocardiography (ECG) half an hour after treatment, of the hyperkalaemia .....

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ix) Repeat ECG 1 hour after treatment of the hyperkalaemia .....

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APPENDIX III

CODE BOOK

Electrocardiography

0 = Normal

1 = Tall peaked T-waves

2 = Tented normal sized T-waves

3 = 2 + Flattened and broad P-waves

4 = 1+ prolonged QT interval and widened QRS and depressed ST segment

5 = 2 + WIDENED QRS

6 = 1 + Prolonged PR interval + widened QRS + depressed ST segment + flattened and broad P-waves

7 = Prolonged QT interval + widened QRS

8 = Not done

9 = Widened QRS

10= 1+ flattered and broad p-waves + prolonged PR interval

11= 10+ prolonged QT interval + depressed ST segment.

12= 2+ prolonged QT interval + widened QRS

13= 1 + prolonged PR interval

14= 2 + prolonged PR interval

16= 10 + prolonged QT interval

17= 1+ widened QRS + depressed ST segment

18= 2+ prolonged PR interval + flattened and broad P-waves.