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RESEARCH ARTICLE

PHARMACOLOGY

SALBUTAMOL NEBULIZATION IN THE TREATMENT OF HYPERKALEMIA

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ABSTRACT

Thirty patients with hyperkalemia (serum K+ levels > 5.5 meq/l) due to severe renal failure were included in the study.10mg salbutamol was given as nebulization over 10 mts in a propped up position through face mask and patient encouraged to take deep breath. Serum potassium levels at 0,1,4 and 6 hrs, ECG before and after nebulization, Serum Glucose, Blood urea, Serum Creatinine, Pulse which were recorded in a bi-hourly basis showed a reduction in Serum K+. Also ECG showing Tall T waves were reverted to normal and conduction blocks disappeared. Thus, salbutamol nebulization is an effective tool in the emergency management of hyperkalemia with ease of administration, technical simplicity, good tolerability without significant adverse effects, quick initial correction of hyperkalemia either as initial monotherapy or in combination with other modalities as a temporary measure for transcellular shift of K+ until a definitive therapy like hemo-dialysis could be instituted.

KEYWORDS

Hyperkalemia, Beta 2 agonist, Salbutamol Nebulization, Cardiac Arrhythmias

INTRODUCTION

Amongst all electrolyte abnormalities "hyperkalemia" associated cardiac arrhythmias (including asystole and ventricular fibrillation) are most serious and lethal. Being a major intracellular constituent potassium affects all cellular functions, well observed in cardiac, skeletal and renal tissues.

Common clinical situations where hyperkalemia occurs are acute renal failure, chronic renal failure, diabetes mellitus, excessive use of potassium sparing drugs (diuretics, ACE inhibitors) and overenthusiastic therapy with potassium containing drugs, adrenal deficiency and acidosis.

Measures known to reduce blood potassium levels result either in a redistribution or elimination of potassium from the body. Measures that tend to effect a redistribution of potassium are insulin + glucose infusion, sodium bicarbonate and beta-agonists like salbutamol .

Measures that result in actual reduction in potassium levels include Dialysis, mainly haemodialysis, the gold standard therapy, and the use of cation exchange resins like sodium polysterene sulphonate.

Salbutamol , a selective beta-2 agonist, lowers serum potassium level on intravenous administration.[6,7,8,9,10] This study is conducted to observe the effect of salbutamol nebulization in the management of hyperkalemia.

PATIENTS AND METHODS

PATIENTS: The patients of renal failure with hyperkalemia .

INCLUSION CRITERIA: Patients with severe renal failure and elevated serum potassium levels (>5.5 meq/lit) were included in the study.

EXCLUSION CRITERIA: Patients were excluded from participating in the study if they had active ischaemic heart disease (angina pectoris and arrhythmias), if they were receiving therapy with Beta- blockers, or if there were technical reasons preventing the delivery of salbutamol through a spacer device and patients with hypersensitivity to salbutamol.

SELECTION: Random selection.

Diagnosis is confirmed and preliminary renal parameters taken.

STUDY DESIGN: OPEN LABELLED STUDY.

DRUG: Salbutamol Respirator solution.Asthalin respirator solution is an acqueous, colourless solution of salbutamol sulphate I.P. adjusted with acid to ph 3.5.

Dilution: Asthalin Respiratory Solution may be diluted with sodium chloride injection IP (normal saline). Solutions in nebulizers should be replaced daily.

Presentation: Bottle of 15ml in a carton.

Salbutamol 10 mg Nebulization in 10 minutes

DESIGN: Thirty patients with hyperkalemia of varied etiology were included in the study, after confirming hyperkalemia in a random choice. ECG and renal parameters were noted. 10 mg salbutamol was given as nebulization over 10 minutes in a prop up position through the face mask applied firmly to the face and patient encouraged to take deep breath. No other drug known to affect potassium level was given. A separate record of cases of hyperkalemia treated with salbutamol was maintained. A large-bore cannula was inserted into an antecubital vein to allow repeated blood sampling.

Biochemical parameters were obtained within one hour using an automatic random access analyzer. Serum potassium level was obtained using an (ion-selective electrode with a 1.1% co-efficient of variation). The patients were monitored throughout the entire measurement period. The pulse rate was measured twice in one hour, and ECG was taken after the restoration of normal pattern on the monitor. Arterial blood gas analysis was done in a few selected patients who presented with the features of metabolic acidosis.

The following were assessed: - serum potsassium levels 0, 1, 4, and 6 hrs

Recording of ECG before and after restoration of normal ECG pattern on the monitor.

OBSERVATIONS

Thirty two patients with hyperkalemia due to renal failure and end stage renal disease were studied. Out of 32 patients two patients were excluded as there was no response in serum potassium following nebulisation. They were labeled as nonresponders and excluded from further study and calculations. Among the remaining thirty patients twenty nine were suffering from chronic renal failure with various comorbidities and one patient had acute renal failure. Both the non responders were chronic diabetics receiving ACE inhibitors.Twenty three were males and seven were females.

Age distribution is in between 39 yrs to 70 years with a mean age of 50.56 years. Fourteen were in the age group of 40-49 yrs, twelve within 50-59 years, two patients between 60-69 years and one aged below 40 yrs and another was 70 yrs old. None belong to paediatric age group.

Among 30 patients 8 were asymptomatic. (26.66%). 22 showed varied symptoms related to both their underlying disease and symptoms pertaining to hyperkalemia. (73.34%). 7 (23,34%)complained nausea, vomiting , head ache and dizziness. 2 patients showed improvement in their symptoms following nebulization. Palpitations were complained by 3 patients and 1 improved after treatment. One patient who was asymptomatic had transient palpitations following nebulization. Generalized weakness was complained by 5 patients Out of them 2 showed improvement. Paraesthesias were found in 3 cases among whom only one had relief. Transient flaccid quadriparesis was seen in one patient who showed improvement in power with ability to move his legs12 hrs following nebulization. Total motor power was recovered by the following day. Breathlessness was observed in 5 cases and 2 became comfortable after nebulization. Acidotic breathing was seen in one patient, who did not register any change. ABG showed metabolic acidosis in this case. Chest discomfort was complained in 2 patients and one was relieved of the discomfort.

Table 1
Clinical Symptoms

Symptoms	before nebulization	following nebulization
Asymptomatic	8	1 transient palpitations 7 remained asymptomatic
Symptomatic	22	
Nausea and vomiting	5	1 improved
Head ache and dizziness	2	1 improved
Palpitations	3	1 improved
Weakness	5	2 improved

Paraesthesia	3	1 improved
Transient flaccid quadriparesis	1	partial improvement in 12 hours with full recovery following day
Breathlessness	5	2 comfortable
Acidotic breath	1	no change
Chest discomfort	2	one comfortable

Of the 30 cases One patient suffered from acute renal failure and 29 had chronic renal failure of varied aetiology and associated co morbid conditions.

Out of 30 cases 17 had hypertension (males 14 : females 3). 12 patients had associated Diabetes mellitus. Old ischaemic heart disease was noted in 2 patients. One female patient had associated valvular heart disease mitral stenosis and mitral regurgitation , compensated. One patient was suffering from nephrotic syndrome. One patient besides diabetic nephropathy also had dilated cardiomyopathy with existing left bundle branch block. One patient had left ventricular failure along with hypertension and chronic renal failure. Flaccid quadriparesis was seen in one patient. H/O intake of angiotensin converting enzyme inhibitors was noted in 13 patients. Aldosterone antagonists were prescribed for cirrhosis in one case of chronic renal failure. One patient of diabetic nephropathy had gangrene of foot. Another patient of poorly controlled diabetes had abcess in gluteal region. Incidental comorbidities like Filariasis of leg is seen in one patient of chronic renal failure with metabolic acidosis, asymptomatic gall stones in one case. Both the nonresponders excluded from study were diabetics on long term usage of ACE inhibitors. (see table 1)

Pulse rate and blood pressure were recorded in all the cases. Respiratory rate was counted for one minute in all the cases. All the patients tolerated the nebulization barring one patient who had transient palpitation which did not necessitate discontinuation of therapy. No tremors, or sweating or signs and symptoms of hypoxia or ventilation perfusion mismatch were encountered during or following nebulisation. Patients with initial K of >9 were not withheld of other modes like calcium gluconate injection which does not modify serum potassium

Blood glucose was done in all cases. Mean blood glucose was 206.75 mg/dl in pre existing diabetics . whereas it is 120.61 mg/dl in non diabetics. Mean for whole group is 155.06 mg/dl. Rise in glucose level was noted in five cases following nebulisation, three were found to be suffering from pre-existing diabetes. Mean blood urea 137,33 mg/dl and Mean creatinine was 9.46 ranging from 1.3 to 14.9. Mean sodium value was 135 mmol /l and chloride was 109 mmol/l.

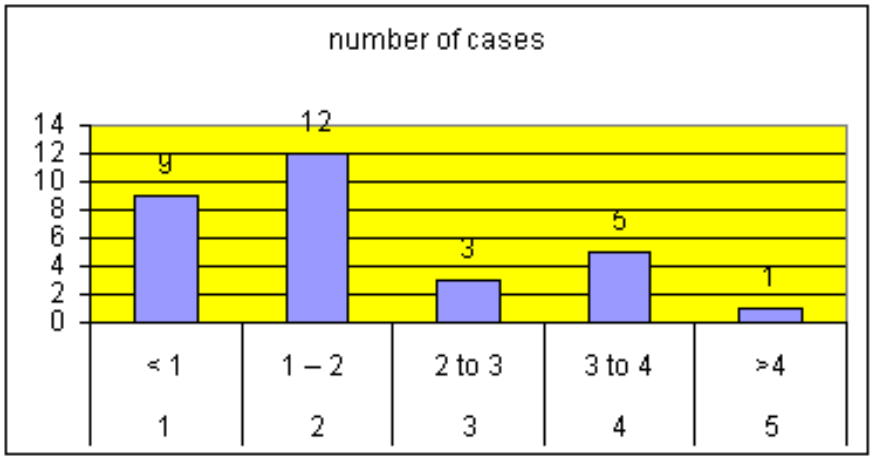
Serum potassium done prior to treatment i.e., K 0 ranges from 5.5 to 10.4 mg% with mean value of 7.055.

All patients showed a reduction in serum potassium level ranging from 0.15 to 4.6 with a mean value of 1.636. Reduction of < 1 meq in 9 cases, 1-2 meq/l in 12 cases, 2-3 meq/l in 3 cases, 3 – 4 meq/l in 5 cases and greater than 4 m.eq in one case.

Table 2
Reduction in serum potassium levels in diabetics and non diabetics

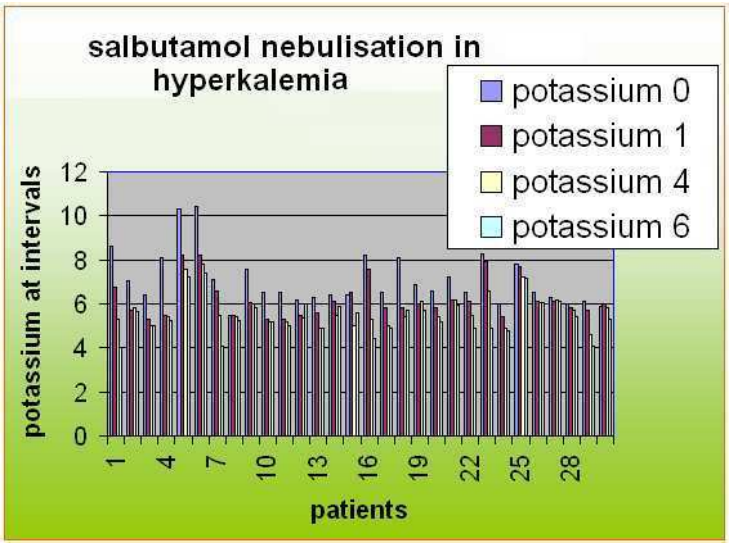
Sl no	reduction in m.eq/l	Diabetics	Non diabetics	Total number of cases
01	< 1	5	4	9
02	1 – 2	7	5	12
03	2-3	-	3	3
04	3 – 4	-	5	5
05	>4	-	1	1

Graph 1
Reduction in k+ levels



Reduction was noticed after one hour of nebulization and continued for six hours. Higher the initial value, greater was the decline in the post nebulization value. One case showed an initial rise in first hour followed by a steady fall in potassium level. Mean Serum potassium after one hour of nebulisation was 6.204 with mean reduction of 0.851 with a range of fall from –0.1 to +2.26. Mean serum potassium after 4 hours is 5.695 with a mean reduction from K 0 of 1.36 ranging from 0.12 to 3.3. Mean serum potassium after 6 hours is 5.429 with a mean reduction from K 0 of 1.626 ranging from 0.15 to 4.6. The decline in the mean potassium concentration from 0-1hr, 1hr-4hr ,and 4hr-6hrs were 0.851, 0.5, and 0.26 respectively. Hence the decline was maximum in the 1st hour to 90 mts. Hence post nebulization reduction of potassium was maximum upto four hours, though it continued upto six hours. (see table 2 and graph 1)

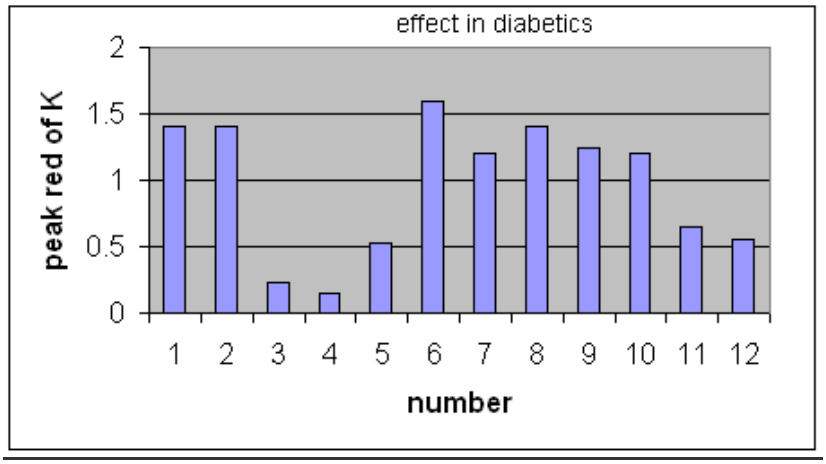
Graph 2
Salbutamol nebulization in Hyperkalemia



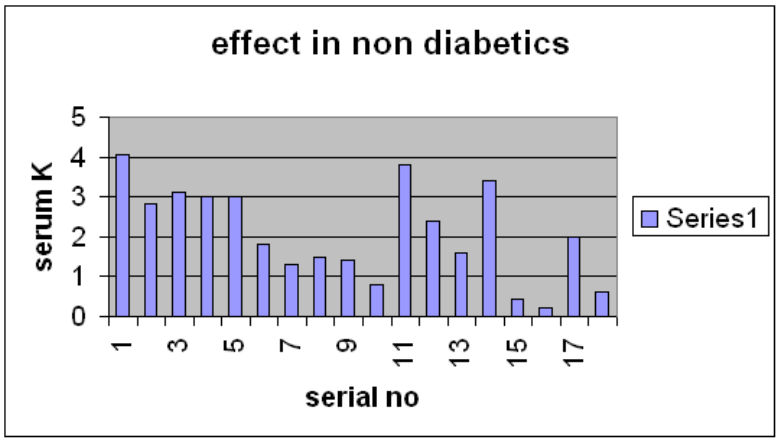
Decrease in serum potassium in Acute renal failure case is 3 meq while average reduction in chronic renal failure cases is 1.588 m.eq/litre.

When comparison was made between diabetics and non-diabetics, the former showed a decline in mean serum potassium of 0.963 with a range from 0.15 to 1.6 whereas nondiabetics showed a reduction in mean serum potassium of 2.067 with a range from 0,2 to 4.06 mmol/l with a difference of more than 1 meq/l. (see graph 3 and graph 4)

Graph 3
Effects in diabetics



Graph 4
Effects in non diabetics



Electrocardiographic changes were found in 24/30 patients. Tall t waves were the most common findings seen in 17/30 cases. 6/30 showed conduction blocks. First degree heart block was seen in 3/30 cases with prolongation of P-R interval. Two cases had left bundle branch block and one case showed right bundle block. Ectopics were seen 4/30 cases. Decrease in P wave amplitude observed in 3/30 cases. One patient had idioventricular rhythm. Poor progression of R- wave in anterior leads was seen in one patient with metabolic acidosis. Tall T waves reverted to normal in most cases and conduction blocks disappeared. One case of chronic renal failure with hypertension, diabetes, dilated cardiomyopathy and nephropathy with left bundle branch block did not change probably due to pre-existing cardiac pathology . (see table 3)

Table 3
ECG Changes

ELECTROCARDIOGRAPHIC CHANGES	NO OF PATIENTS
NORMAL	06
ECG disturbances	
Tall t waves	13
absent p waves	03
Conduction defects	
First degree heart block	03
left bundle branch block	02
right bundle branch block	01
Arrhythmias	
Ectopics	04
idioventricular rhythm	01
Others	
poor progression of r in ant leads	01

DISCUSSION

Hyperkalemia is an important electrolyte abnormality encountered in clinical practice as it is associated with life threatening cardiac arrhythmias like cardiac asystole and ventricular fibrillation. It can be clinically silent until it presents with life threatening manifestations(56). Besides cardiac tissues, skeletal muscle is also affected leading to muscle weakness and paralysis. Often it is sudden in onset involving proximal musculature. In view of its cardiac effects hyperkalemia is a high risk setting demanding an immediate prompt, safe, effective and aggressive management. Electrocardiographic changes may be absent even when hyperkalemia is severe, and therefore normal ECG does not make laboratory confirmation unnecessary(56). In our study we had a small but significant number (6) of patients with hyperkalemia with no electrocardiographic abnormalities. There are different modalities of treatment which either redistribute or eliminates potassium from the body(54) . Among the measures that tend to effect the redistribution of potassium in the body, intravenous insulin and dextrose infusion is well known and most practiced. I V calcium gluconate brings about rapid change, with early onset of action. Intravenous soda bicarbonate is ineffective unless there is coexistent acidosis and beta agonists in oral, intravenous and nebulised routes which are not very familiar. Among those that result in absolute reduction in potassium level are dialysis both haemo and peritoneal . Haemodialysis is more effective among the both and is considered gold standard therapy for hyperkalemia. Cation exchange resins also eliminate potassium from the body but are useful only in non-emergent situations.

The use of sympathomimetics to lower the serum potassium dates long back when it was found that adrenaline (non selective alpha and beta stimulant) may lower the serum potassium levels (35). Nevertheless, this drug was not accepted as a clinical remedy for hyperkalemia , perhaps due to its potential overwhelming side effects. Recently several publications have addressed the issue of lowering serum potassium levels using Beta agonists (4,5,6,7,8,9,10,11,12,13,14,15,16,47,48,49,50). Salbutamol lowers the serum potassium level by the selective activation of beta 2 receptors through the induction of ADP-AMP and opening Sodium potassium pump. The net result of this action is a net movement of extracellular potassium into the cells. Another mechanism suggested is that mediated by serum glucose levels, through its effect on gluconeogenesis and glycogenolysis in the liver. (by increasing the plasma insulin level (9,36,51)

A literature search of medline, upspiral and pubmed and emj online along with standard medical and nephrology text book references was made. References from the articles recovered were searched for the relevant studies. The ideal design of a study of treatment of hyperkalemia is one that is randomized , blinded, and controlled against a placebo or standard therapy. A summary of studies show that most of them are either open label studies and a few have cross over design. Two studies compared nebulization with placebo and the plasma potassium levels in these studies were relatively low and it was expressed by the investigators that it would be unethical not to treat severe hyperkalemia(53).

Most studies examined patients with chronic renal failure. Our study included patients with chronic renal failure except one case suffering from acute renal failure. Except for the studies which were done in paediatric group alone (Singh et al (44) the average age of the patients was more than 50 years. The mean age calculated in our study is 50.56 years

in concordance with most studies. All studies excluded patients on beta blockers and most excluded patients on digoxin. Patients with active ischaemic heart disease, and those on beta blockers , and those in whom there is technical difficulty in administering nebulization were excluded from our study.

Our study was undertaken to observe the efficacy of salbutamol by nebulisation in the management of hyperkalemia. 30 patients of hyperkalemia with serum potassium levels above 5.5 meq/l, associated with renal failure were included in the study after confirming the diagnosis in a random choice. Open label study was taken up as placebo control would be unethical in view of patient's safety as denying treatment may lead to life threatening arrhythmias. Salbutamol 10 mg was given by nebulizer over ten minutes in propped up position by face mask firmly held and patients were encouraged to take deep breath.

Salbutamol may be administered by intravenous route (57,8 ,6,62,9,7,10) as metered dose inhaler(7,8,11,12,13,14,15,16,53) or wet nebulisation(11,6,61,7,38) to bring about reduction in serum potassium. IV therapy might be preferred in crf patients requiring a rapid lowering in plasma potassium, nebulization on the other hand should be preferred in crf patients with coronary artery disease.(36) Salbutamol nebulization though slow is preferred in patients with ischaemic heart disease(36) , and in paediatric population(7,26) for reasons obvious. In a comparative study of IV and Nebulized salbutamol by McClure RJ, Prasad VK, Brocklebank JT in paediatric population it was observed that though the mean initial fall in potassium level within 30 minutes was more with IV , sixty minutes after the second dose, the reduction in the plasma potassium concentration was greater with nebulized salbutamol. There was a significant difference between the two methods of administration at 300 minutes after the first dose, favouring nebulization.(7). No significant adverse cardiovascular effects are seen following salbutamol nebulization (11)and the rise in heart rate was though significant after both nebulization and intravenous infusion , was less after nebulization(6) than after infusion. In our study we have included patients with old ischaemic heart disease where nebulised salbutamol administration did not have any significant change in heart rate and blood pressure in concordance with study by Liou HH et al (however, patients with active coronary artery disease were excluded from our study). Whereas the study by Ho-Jung Kim did not include any case of diabetes (38) , the study by Tanaka Y, Nagao M,Nishio T, Hashida E, KashiwagaA, Shigeta Y. of treatment of hyperkalemia in renal failure with selective beta 2 adrenergic stimulant, terbutaline sulfate included diabetics (7/14 i.e. 50%) intheir study and found that the onset of the plasma potassium lowering effect was slow in diabetics as compared to nondiabetics and more over the potassium lowering effect was more significant in non diabetics)(p value less than 0.01). In our study we had twelve cases of diabetes mellitus out of thirty cases (12/30 I,e. 39.3%) and the reduction in plasma potassium level was definitely more in non diabetics as compared to diabetics.(40) (0.963 in diabetics versus 2.01 in non diabetics) which is statistically significant.

The mean initial potassium for 30 patients is 7.055 meq/l and the mean potassium at 6 hours is 5,429 with a mean reduction of 1.626. When data is analyzed in female patients numbering 7/30 it was observed that the mean reduction is 2.0 meq/l compared to 1.626 in total number. Mean initial potassium however is 7.5714 i.e., 0.51 meq higher than average. In one of the studies it was noted that mean peak salbutamol serum level achieved is higher in females compared to males following inhalation. Whether this observation of higher reduction in females compared to males is as a result of higher initial potassium, or a better serum salbutamol achieved in females needs to be evaluated with a bigger sample size and serum estimation of salbutamol.

Other beta 2 agonists like fenoterol (50) and terbutaline may also be used to lower the serum potassium levels. The use of inhaled salbutamol has been advocated to shift the potassium into the cells and lower the serum potassium levels by 1 – 1.5 meq /litre The authors of several clinical trials conclude that this drug administered with nebuliser or i.v. is as effective , rapid and safe treatment of hyperkalemia in children and advocated its use as first line emergency treatment for this disorder in their centers.(7,9,11,39,,56,57)Salbutamol may be administered as sole therapy or in combination with Insulin glucose therapy which seems to protect against insulin induced hypoglycemia (37). Another advantage of this combination is that the salbutamol administration may repeated, unlike the insulin glucose therapy which is associated with hypoglycemia. IV salbutamol is as effective as Insulin Dextrose infusion and normalization of hyperkalemia on electrocardiogram noticed within one hour as noted in the study Ngugi NN, Kavima JK, et al.(37)The transcellular hypokalemic effects of salbutamol was seen to be enhanced by the simultaneous administration of sodium bicarbonate which by itself could not lower the plasma potassium level. This was related to the activation of Na-K pump with acute correction of underlying metabolic acidosis.(38) But Allon M Shanklin N study of Effect of bicarbonate administration on plasma potassium in dialysis patients; interactions with insulin and albuterol, suggests that bicarbonate administration does not potentiate the potassium lowering effects of insulin of albutterol in hemodialysis patients (61).

Whereas intravenous route has prompt response within 15 mts, inhalation was found to be effective in 60 – 90 mts. Sample size in the studies conducted with intravenous salbutamol ranged from 11- 24 and the dose administered was around 0.5 mg and the mean initial potassium ranging from 5.53 to 7.02 m mol/l.

Serum salbutamol was not measured in any of the study. The peak reduction in potassium ranged from 0.87 to 1.69 and the time of maximum reduction was around 30 mts, in most of the studies (Murdoch IA et al, Montoliu J et al, Liou H H et al). Kemp et al found the maximum reduction was at 120mts. The reduction in potassium level is proportionate to the initial potassium in most of the studies. Salbutamol serum assay could not be done in our study due to paucity of facility. From our study it is clear that higher the initial potassium level, greater was the reduction in mean potassium level. But in the study by Leanza HJ, Rivarola G, Graciela Garcia M,Najun Zarazaga CJ, Casadei D. of “rapid correction of acute hyperkalemia with nebulized salbutamol” no correlation was found between the grade of hyperkalemia and the magnitude of plasma potassium decrease after therapy.

In the study by American college of chest physicians it is found that there was an initial elevation of serum potassium followed by sustained fall. This paradoxical elevation is noted when full dose was given within 2 minutes. (53) Serum potassium was done in the early minutes registered a rise, followed by significant decrease after 5 minutes onwards. Most articles from literature recorded plasma potassium 30 mts following the administration (8,9,10.11,12,13,14,15) They did not find this observation. This initial rise was supported by Du Plooy et al (46) may point to an alpha stimulating effect by this agent. In our study one case showed transient initial rise at 1 hr followed by a steady fall . This difference was found to be significant by Fischer’s exact test. Clinical significance of this paradoxical effect is left for further evaluation. Nevertheless this finding has to be addressed in view of the potential life threatening hazards of hyperkalemia. It is recommended to administer calcium , before salbutamol, for its rapid onset of action and to avoid the potential deleterious effects of this paradoxical early rise, though it sounds theoretical. This is so, because there

is already an existing high adrenergic tone in this subset of patients. In all our cases we preferred to continue with initial calcium gluconate administration when serum potassium is > 8 meq , which would protect against arrhythmias by its membrane stabilizing effect, and noninterference with serum potassium estimation later.

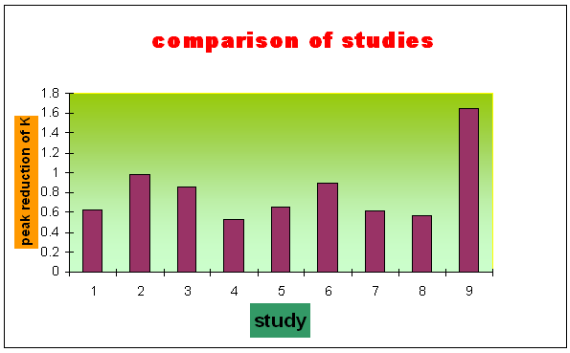
Serum glucose estimated post nebulisation reveals modest but significant change in 5 patients, 3 of them were diabetics, and 2 non-diabetics. Similar finding is observed by Montoliu et al(8) in blood glucose following 15 mgs of salbutamol nebulised over a period of 30 mts. , Allon M Copkney etal(11) and Chiang et al(6) also observed rise in serum glucose in their patients post nebulization and commented that this would be beneficial in strategy of co-administration with insulin-dextrose infusion where insulin induced hypoglycemia could be averted. Hence this combination would be more effective especially when the patients are non-diabetics.

In one case which presented with flaccid paralysis, there was partial restoration of power in 12 hrs, with full recovery on the following day with normalization of potassium similar to that described by Gotze et al (52). The other case did not show any improvement.

Table 4
Comparison of present study with other studies

No	Study	sample size	dose	ini K	peak red	max act	duration
1	Allon M.Dunlay R.Copkney 1989	10	10 mg	5.93	0.62	90 mts	>120 mts
2	Allon M.Dunlay R.Copkney1989	10	20 mg	5.81	0.98	90mts	>120 mts
3	Liou HH.Chiang SS.WuuSC etal	15	10mg	5.66	0.85	90mts	>180 mts
4	Allon M.Schanklin N.	5	10mg	4.29	0.53	60 mts	>60mts
5	Allan M Copkney C. 1990	12	20 mg	5.56	0.66	60 mts	>60 mts
6	Montoliu J , Almirall J.PonzE et al	10	15 mg	6.5	0.9	30 mts	>360 mts
7	McClure RJ.Prasad VK. Et al	11	2.5 mg	5.9	0.61	30 mts	>300 mts
8	Kim H J et al	9	15 mg	5.99	0.57	60 mts	>60 mts
9	Present study	30	10 mg	7.055	1.644	90 mts	>360 mts

Graph 5
Comparison of studies with present study



COMPARISON OF STUDIES WITH NEBULIZED SALBUTAMOL

As tabulated supra the eight studies with nebulised salbutamol had a sample size of 10.25 per study and the dose of salbutamol nebulized is 11.56 mg on average. The mean initial potassium in the above studies is around 5.705 and the mean reduction noticed is 0.715 with a range of 0.53 to 0.98. The sample size in our study was much higher i.e., 30 and the mean initial potassium was 7.055 and the mean reduction was 1.626 with a p value of >0.001 denoting the reduction is highly statistically significant. Period of Maximum reduction noticed in most studies was at around 60- 90 mts which probably corresponds to peak concentration achieved at 11/2 hrs (63). In our study maximum reduction was noticed after 60 mts which is in concordance with earlier studies. The slope of reduction is exponential with a reduction in 1st hour – 0.851, next 3 hrs –0.5, last 2 hrs—0.26. Hence the effect is noticed for > 360 mts. This is in concordance with Montoliu etal who noticed for >360 mts. Whether this hypokalemic effects continue further needs to be evaluated. However if dialysis could not be instituted early enough it seems reasonable to repeat treatment after 6 hrs to sustain the effect as commented by Ngugi NN etal., (37). As understood from the knowledge of salbutamol biometabolism and plasma half life(6 –8 hrs) it is natural that expected decline in the effect of potassium reduction wanes off with time and a second dose of nebulization could be repeated after 6 – 8 hrs which sounds scientific and technically convenient until a definitive measure could be instituted. (see graph 5)

SUMMARY AND CONCLUSIONS

Following conclusions are arrived after a critical analysis of this study comparing with those of earlier experiences.

1. Salbutamol nebulization is an effective and a convincing handy tool in the emergency management (treatment) of hyperkalemia
2. Ease of administration, technical simplicity and good tolerability without significant adverse effects make it a good option in management of hyperkalemia. Nebulisation is preferred over intravenous administration in cardiac patients due to low incidence of cardiovascular side effects.
3. It avoids early delay in the initiation of hypokalemic management with dialysis. It can be used as initiation monotherapy or can be combined with other modalities , as a temporizing measure for transcellular shift of potassium, until a definitive therapy like haemodialysis could be instituted.
4. Prompt in action with longer duration of hypokalemic effects.
5. Could be repeated after 4-6 hrs if required.
6. Combination with insulin-dextrose therapy would be beneficial in averting insulin induced hypoglycemia particularly in diabetics with chronic renal failure.
7. Combination with acidotic correction by bicarbonate in patients with metabolic acidosis potentiates the effect of bicarbonate, which independently is ineffective in lowering serum potassium.
8. However the drawback is that effect of salbutamol is not always predictable as seen in this study where 2/32 were non-responders.
9. Though early rise following nebulisation is clinically insignificant , still remains a risk , needs to be protected by prior administration of membrane stabilizer like calcium gluconate.
10. Much elaborate correlative studies with estimation of serum salbutamol and potassium at 3mts, 1 hour, 4 hrs, 6hrs and

a sample after 6 hrs would throw more light on the efficacy of salbutamol.

11. Estimation of serum insulin along with serum glucose in the patients prior and post nebulization would clear the enigma surrounding the dual effects of increased glucose through its action on the liver, increased insulin through its action on intact beta cell population. It also clears which mechanism is dominant and clinically significant.
12. Though effective the reduction is relatively less pronounced in diabetics.
13. It may be avoided in patients with unstable coronary artery disease.

BIBLIOGRAPHY

1. Saxena K clinical features and management of poisoning due to potassium chloride Med Toxicol Adverse Drug Exp. 4, 429-443 (1989) (ISI) (Medline).
2. Andrews, SB (1990) Disorders of potassium homeostasis. Paediatric clin North An 37, 419-427 (ISI)
3. Rosa, RM, Silva, P-Young, JB et al (1980) Adrenergic modulation of extrarenal potassium disposal N Engl J Med 302, 431-434 (Abstract
4. Landborg, P. (1983) Adrenergic blockade on potassium concentration in different conditions. Acta Med Scand 672 (Suppl), 121-125
5. Clausen, (1983)Adrenergic control of Na-K homeostasis, Aeta Med Scand 672 (suppl) 111-115
6. Liou, H H, Chiang, SSWU, SC, et al (1994)Hypokalemic effect of IV infusion or nebulization of salbutamol in patients with chronic renal failure, Am J Kidney Dis 23, 266-271 (ISI) (Medline
7. Mc clure, RJ Prasad, VK, Brockleback JT(1994) Treatment of hyperkalaemia using Intravenous and nebulized salbutamol Arch Dis. child 70, 126-128 (Abstract).
8. Montoliu, J, lens , XM, Revert, L (1987) Potassium-lowering effect of albuterol for hyperkalemia in renal failure Arch Intern Med 147, 713- 717 (Abstract)
9. Kemper, MJ, Harps, E, Muller- Wiefel, DE (1966) Hyperkalemia; therapeutic options in acute and chronic renal failure, clin Nephrol 46, 67 -69.
10. Leich, Ag, Clancy, LJ, Costello, JF, et al (1976) Effect of Intrainfusion of salbutamol on ventilatory response to carbondioxide and hypoxia and on heart rate and plasma potassium in normal men.Br Med J, 365-367 (Medline)
11. Allon, M, Dunlay, R, Copkney, C (1989) Nebulized albuterol for Acute Hyperkalemia in patients on haemodialysis. Ann Internal Medicine 110, 426-429. (ISI) (Medline).
12. Bennet, AJ, Tattersfield, AE (1997) Time course and relative potency of systemic effect from salmeterol and salbutamol in healthy subjects, Thorax 52, 458-464 (Abstract).
13. Lipworth, BJ, clark, DJ, Koch, P et al (1997) Pharmacokinetics and extrapulmonary B2 adrenoceptor activity of nebulized racemic ssalbutamol and its R and S isomers in healthy volunteers, Thorax 52, 849-852 (Abstract)
14. Millar, EA, Connell, JMC, Thomas, NC (1997) The effect of nebulized albuterol on the activity of the renin- angiotensin system in asthma. chest 111, 71-74 (Abstract/ Free full text).
15. Brenner P, Burgess, C Beasley, R, et al (1992) Nebulized fenoterol cause greater CVS and hypokalaemic effects than equivalent bronchodilator dose of salbutamol in asthmatics. Res. Med. 86, 419-423 (ISI) (Medline).
16. Crane, J. Burgess, C, Beasley, R (1989) Cardiovascular and hypokalaemic effects of inhaled salbutamol, fenoterol and

isoprenaline. Thorax 44, 136-140 (Abstract).
17. some evidence that potassium influx or reduced efflux from cells is direct effect of insulin. Goldflals et. al (1976)
18. Albuterol and other Beta adrenergic agents induce the intracellular movement of potassium via the stimulation of sodium potassium ATP pump.Article by Mary W Lieh- Lai, MD 2003
19. Lockwood et . al (1974), Petit et. al (1974) and Wang et.al (1976)
20. A 0.6 m.mol/lt change in plasma potassium for each 0.1 unit change in pH. Brunnel et al, 1956
21. A large no. of factors other than change in hydrogen ion concentration effect distribution of potassium in acid base disorders. Androuge and Medias, 1981
22. Hyperkalemia by A.D. A. M. Int. http:// health, Yahoo. com/ health/ ency / Adam/ 001179/ overview
23. http://e medicine. com/ ped/ topic 1026. htm
24. Harrison- textbook of internal medicine,(16th edition) page no. 263
25. Basics of renal failure (Pathophysiology and management) by Dr. R. Narasimha Murthy (MD., Gen Med.)F.Card (SAMS).
26. Blumberg, A. Weidmann, P. Shaw, S, Gnadinger, M. Effect of various therapeutic approaches on various plasma potassium and major regulating factors in terminal renal failure, Am J Med 1988; 85; 507
27. Rose BD, Clinical physiology of Acid-Base balance and electrolyte disorders, 4th edition., Mc. Graw- Hill, New York, 1994, pp 848-852.
28. Nolph, KD, popovials, RP, Qhods, AJ, Twardowski, Z. Determinants of low clearance of small solutes during peritoneal dialysis, kidney Int. 1978, 13. 117
29. Hou, S, Mc Elroy, PA, Nootens, J, Beach, M.Safety and efficacy of low-potassium dialysate, Am J. Kidney Dis 1989, 13,13
30. Morrison, G, Michelson, EL, Brown, S. Morganroth, J mechanism and prevention of cardiac arrythmias in chronic hemodyalysis patients, kidney int. 1980, 17, 811
31. Substitution in the amino group of catecholamines contribute to potency at beta receptors with decreased activity at alpha receptorsand decreased metabolism by MAO.Nelson 1982
32. Aerosol administration leads to effective activation of beta 2 receptors in the bronchi but very low systemic drug concentration. New house and Dolovich 1986
33. Lens, XM, Montoliu, J, Casee, A et. al (1989)Treatment of hyperkalemia in renal failure. Salbutamol vs. Insulin, Nephrol Dial Transplant 4, 228-232 (Abstract)
34. Clausen, T, Events, Mc (1989) Regulation of the Na-K pump in skeletal muscle. Kidney Int. 35, 1- 13 (ISI) (Medline)
35. D'silva, (1934) The action of adrenaline on serum potassium J Physiology 82, 393-398.
36. Liou HH, Chiang SS, WC , SC, YANG WC , Hwang TP (Dept. of Medicine Veterans General Hospital – Taipei, Taiwan R.O.C.)
37. Ngugi NN, Mc Ligevo SO, Kavima JK, Dept of Medicine)
38. KIM H.J. Dept. of Internal Medicine , Hanyang University Kuru Hospital, Korea.
39. Leanza HZ, Rivarola G, Gracida Garcia M, Najun Zarazaga GJ, C asidi Dinstitute de Nefrologia, Buenos Aires, Argentina
40. Tanaka Y, NagaoM, Nishio T, Hashida E, Kashiwagi A, Shigeta Y, A new treatment of hyperkalemia in renal failure with selective beta 2 adrenergin stimulant, terbutaline sulfate.
41. Rey E, Luquel L, Richard MO, Mory B, Offenstadt G, Olive G(Eur J Clin Pharmacology 1989;37(4):387-9

42. EMJ Online Emergengy Medical Journal Original Article Peter Ahee ` and Alexander
43. Stewart GW, Corrali RJ Fyffe JA, Stockdill G, Strong A
44. FSN Journal club Inhaled Albuterol for hyperkalemia in premature neonates, singh BS, Sadiq HF, Noguchi A , et al, J Perinatal 2000 ; 20: 461-2
45. Semmerkrot BA, Monner LA. A warning for the treatment of hyperkalemia with Salbutamol. Eu J Paediatric 1997, 156, 420
46. Du- Plooy, WJ, Hay L, Kahler cp, et al.The dose related hyperkalemia hypokalemia effects of salbutamol and its arrythmogenic potential Br J. Pharmacology 1994: 11173.6
47. Mandelberg A, chan, E, Noviski, N et al (1997) Nebulized wet aerosol treatment in emergency room, is it essential? comparision with large spacer device for metered dose inhaler chest 112, 1501-1505
48. Kung M, Lexington, KY (1986) Parental adrenergic bronchodilators and potassium
49. Wang P, clausen, T (1976) Treatment of attacks in hyperkalemic familial periodic palalysis by inhalation of salbutamol. Lancet
50. Hadboom, JRE, Deenstra, Struyvenberg A(1995) Hypokalemia induced by fenoterol.
51. Clausen, T, Everts, ME (1989) Regulation of Na-K pump in skeletal muscle kidney Int 35,1-13 Medline
52. Gotze (scan. j. pharm 27/5/383-84)
53. American college of chest physian,chest 1999, 115,617,622 Avigdor Mandelberg et al. metered dose inhaler
54. Basics of Renal Failure (Pathophysiology and management) by Dr. R.Narsimha Murthy MD (Gen) F. card (S.A.M.S)
55. CIN-2003 Rajesh. Free papers/communiciones libres/ Medical treatment of Hyperkalemia (IV calcium gluconate, IV sodium bicarbonate, Insulin glucose infusion and salbutamol nebulization)
56. Chronic Renal Failure in children: Georges Ramalanjaona, MD, Dsc,FACEP
57. Murdoch IA, Treatment of hyperkalemia with IV salbutamol , arch Dij child 1991: 67. 527-528
58. Arias- Reyes JA, Malos- Martinez M.Velesquaz Jones I , Dubey-orlega I.A.
59. Kamel`S. Kamel and charles weiNephrol Dial Transplant 2003 18:2215-2218
60. Stewart Mc Morran-Cacl2 EMJ 2001: 18: 233
61. Allon M. Shanklin American journal of kidney diseases 1996 oct 28 (4): 508-14
62. Noyan A. Anarat A. Pirti M, et al Treatment of hyperkalemia in children with IV salbutamol Acta Paediatric jpn 1995;37;355-7 medline
63. Goodman & Gilman's The Pharmacological basis of Therapeutics 11th edition 2005