ORIGINAL ARTICLE

Nebulized salbutamol with or without glucose and insulin to treat hyperkalemia: a randomized controlled trial

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The authors declare no conflict of interest in relation with the present article.

Background and objective: Hyperkalemia is a life-threatening condition that is detected fairly often in the hospital emergency department. Treating hyperkalemia with β_2-adrenergic drugs in association with other agents has been recommended. This study aimed to compare the efficacy of nebulized salbutamol alone or in combination with insulin and glucose to treat hyperkalemia.

Patients, material and methods: Prospective randomized controlled trial enrolling patients with hyperkalemia (potassium level >5.5 mEq/L). Patients were assigned to a monotherapy group (nebulized salbutamol alone) or a combined therapy group (salbutamol plus insulin and glucose). If acid-base imbalance was detected, sodium bicarbonate was also administered. We recorded patient characteristics, medical history, current medication that might cause high potassium concentrations, plasma potassium concentration, and discharge diagnosis. Variables were compared between groups.

Results: Eighty-one patients (40 in the monotherapy group) were enrolled. The mean (SD) potassium concentration at baseline was lower in the monotherapy group (6.35 [0.04] mEq/L) than in the combined-therapy group (6.88 [0.7] mEq/L) (P<.001). Mean potassium levels were significantly lower in both groups 3 hours after treatment, falling to 0.4 (0.7) and 0.59 (0.6) mEq/L, respectively (P<.001 in both comparisons). The posttreatment and initial potassium concentrations were unrelated. No between-group treatment effect on the reduction of plasma potassium concentration was found. Potassium reduction was uninfluenced by the patient's medical history, including the use of medications that potentially lead to hyperkalemia.

Conclusion: The effect of nebulized salbutamol alone on hyperkalemia is similar to the effect of combining salbutamol with insulin and glucose. [Emergencias 2013;25:37-42]

Keywords: Hyperkalemia. Treatment. Salbutamol, nebulized. Nebulized salbutamol. Glucose-Insulin.

Introduction

Potassium disorders are one of the most frequent electrolyte alterations encountered in the emergency department[1], and approximately 10% of hospitalized patients have hyperkalemia[2]. Hyperkalemia may be due to one of three main causes[3]: increased intake and absorption of potassium, renal elimination disorder and transcellular deviations. In the first group of patients, although excessive potassium intake rarely causes hyperkalemia, it can occur when patients with renal failure take potassium supplements, inadvertently or during treatment with potassium-sparing diuretics or angiotensin converting enzyme inhibitors (ACEI). The second group includes cases of acute or chronic renal failure with clearance less than 10-15 mL / min, other nephropathies or hyperaldosteronism. The third group includes patients with metabolic acidosis, insulin deficit and hypertonia, exercise or periodic hyperkalemic paralysis.

Hyperkalemia is a potentially lethal condition which requires early diagnosis and rapid treatment to reduce plasma levels of potassium and avoid potential consequences[1,2]. The recommen-

dations of European clinical guidelines for the treatment of hyperkalemia include withdrawal of the possible culprit drug and administration of ion exchange resins, insulin plus glucose, bicarbonate, calcium gluconate and beta$_2$-adrenergics (β_2)[4,5]. β_2 may be administered in nebulized form or intravenously[2,4]. In our country, the literature on the treatment of hyperkalemia limits the use of salbutamol, nebulized or intravenous, to severe cases of hyperkalemia (serum K> 7.5 mEq / l)[6,7], and it has even disappeared from some emergency medicine manuals[8] or from treatment algorithms despite its usefulness being mentioned in the text[3]. A Cochrane review has shown that nebulized β_2 and insulin plus glucose are the most soundly based treatment options for managing cases of hyperkalemia[9]. However, in an older European review that evaluated the use of different β_2, both nebulized and intravenous, alone or in combination, it was only the third treatment option for hyperkalemia[10]. There is growing consensus that the combination of β_2 associated with insulin plus glucose produces greater reduction of potassium values[4,5,9], so some authors do not recommend the use of β_2 alone for the initial treatment of hyperkalemia[11], although this not evidence-based. We therefore believed it necessary to establish the efficacy of nebulized salbutamol alone in the initial treatment of hyperkalemia. In our country, except for isolated descriptions, this has not been studied[12]. The objective of this study was to compare the effectiveness of nebulized salbutamol alone versus the combination of nebulized salbutamol with insulin plus glucose in the initial treatment of hyperkalemia.

Method

We performed a prospective randomized study of all patients over 18 years with acute hyperkalemia, attended at the ED of a 430-bed university hospital during one year (January to December 2009), defined as serum potassium levels greater than 5.5 mEq/l. We excluded patients with habitual potassium values above this cutoff point. The study was approved by the ethics committee of our hospital.

Patients were assigned in order of arrival to one of two treatment arms: monotherapy with nebulized salbutamol (20 mg of atomized salbutamol, corresponding to 4 cc of salbutamol plus 1 cc of saline) administered with a nebulizer for 10 minutes, or a combination of nebulized salbutamol with rapid insulin plus glucose (10 IU intravenous bolus followed by 50 ml of 50% dextrose administered during 15 minutes). In cases with acid-base balance disorder defined as the presence of a pH below 7.20 and / or serum bicarbonate below 15 mEq / l, we added bicarbonate therapy (50 mEq of 1 M bicarbonate bolus administered during 3 minutes).

Data was collected on age, sex, medical history (hypertension, diabetes mellitus, heart disease, liver disease and chronic kidney failure) and potentially hyperkalemic medication (spironolactone, amiloride plus hydrochlorothiazide, oral potassium and ACEI). Plasma creatinine, sodium, potassium and venous blood gases were determined at patient arrival and again three hours after treatment. We recorded the reduction of plasma potassium and the discharge diagnosis. We then performed a comparison between the two treatment groups. Adequate treatment response was considered a reduction in plasma K equal to or higher than 0.5 mEq/L.

For statistical analysis we used SPSS 15.0 (SPSS Inc., Chicago, USA). To establish whether there were differences in quantitative variables (age and serum creatinine, sodium, potassium, pH and bicarbonate) Student's t test was used for independent data. Categorical variables (sex, addition of bicarbonate, medical history and number of hyperkalemic drugs) were analyzed using chi-square test with Fisher correction when necessary. Finally, to determine differences between groups in blood potassium reduction we used analysis of variance for repeated measures with treatment as the variable factor. Additionally, Student's t test was used for related data in both groups separately to monitor the evolution of potassium measurements. We also evaluated whether the decrease in potassium level was related to the number of hyperkalemic drugs being taken by the patient or their medical history, for which we used single-factor analysis of variance and Student's t test for independent data respectively. A *P* value of less than 0.05 was considered statistically significant for all analyses.

Results

During the study period we included 81 patients diagnosed with acute hyperkalemia. Six patients (7.4%) had no relevant medical history, 27 (33.3%) had had one previous episode, 27 (33.3%) two, 17 (21%) three and 4 (5%) four episodes. Regarding potentially hyperkalemic drugs, 23 patients (28.4%) were not taking any

while 37 (45.7%) were taking one, 20 (24.7%) two and 1 (1.2%) was being treated with three such drugs. The final diagnoses with the cause of hyperkalemia are shown in Table 1.

Forty patients were treated with nebulized salbutamol alone and 41 were treated with the combination of nebulized salbutamol with insulin plus glucose. Five patients (12.5%)in the salbutamol alone group and 13 (31.7%) in the combined treatment group had acidosis and received additional treatment with bicarbonate (P = 0.038). Mean baseline potassium level was 6.35 mEq/l (SD 0.4) in the salbutamol alone group and 6.88 mEq/l (SD 0.7) in the combined treatment group (P <0.001). The baseline characteristics of both treatment groups are shown in Table 2. None of the patients included in the study had ECG changes secondary to severe hyperkalemia, so none required additional treatment.

On excluding patients receiving bicarbonate, the comparative results were similar to those reported above (initial potassium 6.32 mEq/l (SD 0.4) in the salbutamol alone group vs 6.77 mEq/l (SD 0.7)in the combined treatment group; p = 0.003), and there were no differences in the other parameters evaluated (Table 3).

In both treatment groups we observed significantly reduced potassium levels at three hours (Table 4), and no differences in reduction between the two groups (Figure 1). These results were maintained on excluding from the analysis those patients who received bicarbonate (Table 4 and Figure 2).

Potassium reduction was not influenced by the presence or number of diseases, nor by previous administration of potentially hyperkalemic drugs, as shown in Table 5.

All patients showed plasma potassium reduction of at least 0.5 meq/l, so none was considered a non-responder. Only 17 patients (21%) had non-normalized potassium values at 3 hours after treatment, and showed mean final potassium of 6.08 (0.54) meq/l. Of these, four patients were in the salbutamol alone group and 13 in the combined treatment group. Potassium values after treatment were 5.78 (1.5) and 6.17 (0.6) mEq/L respectively.

In both groups, only mild and transient side effects were recorded, with sinus tachycardia observed in 2% of patients. None required treatment or lower doses of salbutamol. Finally, there were no cases of hypoglycemia.

Table 1. Causes of hyperkalemia

	n (%)
Drugs	55 (67.9)
Acute renal failure and drugs	9 (11.1)
Non-obstructive acute renal failure	5 (6.2)
Obstructive renal failure	6 (7.4)
Unknown	6 (7.4)

Table 2. Comparisons between the two treatment groups at baseline

	Salbutamol alone (n = 40) n (%)	Combined treatment (n = 41) n (%)	*p*
Age (years) [mean (SD)]	75.8 (9.2)	73.2 (12.6)	NS
Male sex [n (%)]	22 (55)	18 (43.9)	NS
Addition of bicarbonate [n %)]	5 (12.5)	13 (31.7)	0.038
Medical history [n (%)]			
Hypertension	19 (47.5)	21 (51.2)	NS
Diabetes Mellitus	13 (32.5)	13 (31.7)	NS
Heart disease	21 (52.5)	25 (61)	NS
Liver disease	6 (15)	12 (29.3)	NS
Renal failure	8 (20)	9 (22)	NS
Drugs [n (%)]			
ACEI	17 (42.5)	21 (51.2)	NS
Aldosterone	12 (30)	15 (36.6)	NS
Thiazides	3 (7.5)	2 (4.9)	NS
Potassium aspartate	8 (20)	3 (7.3)	NS
Laboratory tests [mean (SD)			
Initial Creatinine (mg/ml)	3.01 (3.2)	3.01 (2.5)	NS
Initial Na (mEq/l)	134.3 (6.1)	133.7 (5.7)	NS
Initial K (mEq/l)	6.3 (0.4)	6.9 (0.7)	< 0.001
Initial pH	7.5 (0.7)	7.4 (0.4)	NS
Initial Bicarbonate (mEq/l)	19.5 (6.8)	19.7 (4.9)	NS

SD: standard deviation; ACEI: angiotensin converting enzyme inhibitors; NS: not significant.

Table 3. Comparisons between the two treatment groups at baseline, excluding patients receiving bicarbonate

	Salbutamol alone (n = 35) n (%)	Combined treatment (n = 28) n (%)	*p*
Age (years) [mean (SD)]	76.2 (9.4)	72.2 (14.3)	NS
Male sex [n (%)]	20 (57.1)	13 (46.4)	NS
Medical history [n (%)]			
Hypertension	16 (45.7)	15 (53.6)	NS
Diabetes Mellitus	11 (31.4)	8 (28.6)	NS
Heart disease	21 (60)	17 (60.7)	NS
Liver disease	6 (17.1)	9 (32.1)	NS
Renal failure	7 (20)	3 (10.7)	NS
Drugs [n (%)]			
ACEI	16 (45.7)	14 (50)	NS
Aldosterone	12 (34.3)	11 (39.3)	NS
Thiazides	3 (8.6)	1 (3.6)	NS
Potassium aspartate	7 (20)	2 (7.1)	NS
Laboratory tests [mean (SD)]			
Initial Creatinine (mg/ml)	2.49 (2.5)	2.56 (1.4)	NS
Initial Na (mEq/l)	133.46 (5.8)	134.05 (6.4)	NS
Initial K (mEq/l)	6.76 (0.7)	6.31 (0.4)	< 0.01
Initial pH	7.56 (0.7)	7.42 (0.5)	NS
Initial Bicarbonate (mEq/l)	20.57 (6.4)	21.03 (4.6)	NS

SD: standard deviation; ACEI: angiotensin converting enzyme inhibitors; NS: not significant.

Table 4. Differences between initial serum potassium levels and those observed 3 hours after treatment in all patients and after excluding those receiving bicarbonate

	Initial K (mEq/l) Media (DE)	K at 3 hours (mEq/l) Media (DE)	Difference (mEq/l)	*p*
All patients (n = 81)				
Salbutamol alone (n = 40)	6.35 (0.4)	4.94 (0.5)	1.41 (0.7)	< 0.001
Combined treatment (n = 41)	6.88 (0.7)	5.29 (0.8)	1.59 (0.6)	< 0.001
Patients not receiving bicarbonate (n = 63)				
Patients not receiving bicarbonate (n = 35)	6.31 (0.4)	4.92 (0.5)	1.39 (0.7)	< 0.001
Combined treatment (n = 28)	6.76 (0.7)	5.18 (0.8)	1.58 (0.6)	< 0.001

No significant differences were observed in the reduction of potassium between the two treatment groups.

Discussion

The results of this study showed that treatment with nebulized salbutamol alone or in combination with insulin plus glucose significantly reduced plasma levels of potassium, without differences in reduction. Furthermore, underlying diseases or potentially hyperkalemic drugs did not influence the results. The fact that the results did not vary for the subgroup of patients not receiving bicarbonate therapy, i.e. those without acidosis, indicates that both treatment regimes acted similarly regardless of acid-base balance.

These results are consistent with those of other authors on the effectiveness of β_2 for the treatment of hyperkalemia[4,5,9,10,13], which have shown similar efficacy in reducing plasma potassium regardless of the route of administration[13,14] and the type of β_2 used[15].

Although the potassium-reducing effect of nebulized β_2 is dose-dependent 14 and the doses required exceed those commonly administered for the treatment of asthma attacks[14], the typical side effects of intravenous β_2, such as tachycardia, palpitations, tremor and anxiety, are less common when β_2 is administered in nebulized form[2,13], but there could be some differences in the incidence of side effects depending on the type of β_2 used[15].

In contrast to other authors who found greater efficacy with combination therapy compared with

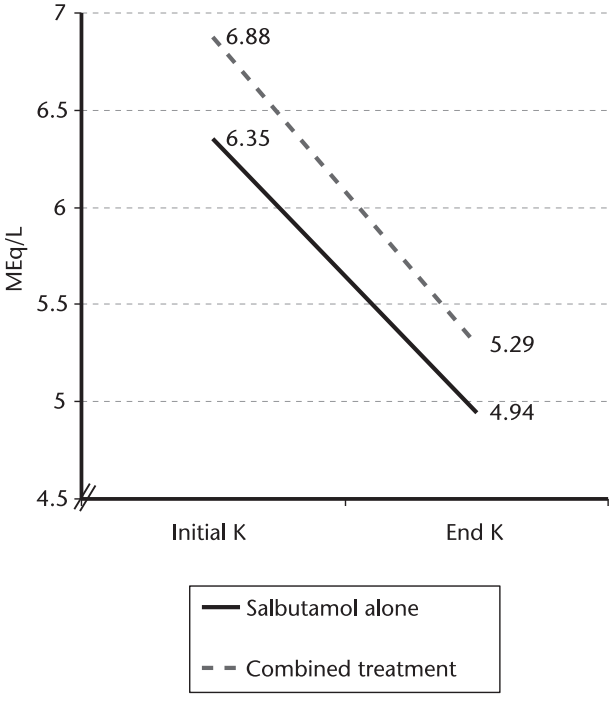

Figure 1. Response to treatment. There were no significant differences in reduction of potassium values between the two groups. End K: Potassium level at three hours after treatment.

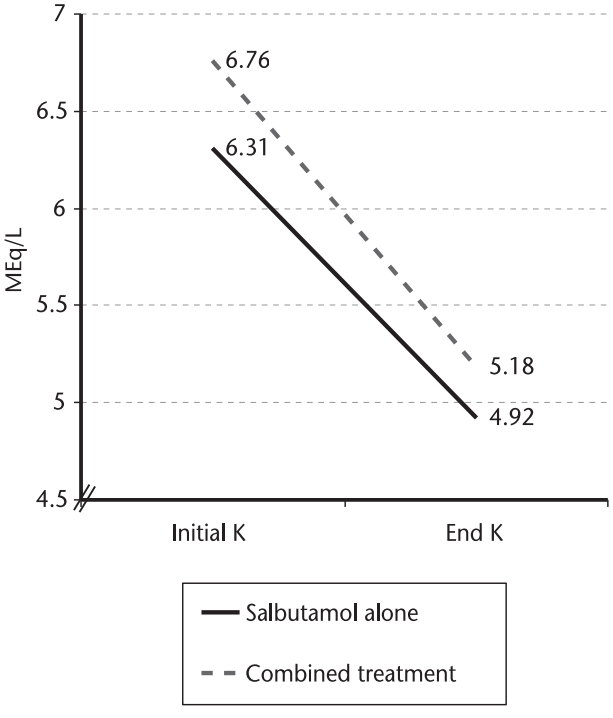

Figure 2. Response to treatment in patients not receiving bicarbonate. There were no significant differences in reduction of potassium values between the two groups. End K: Potassium level at three hours after treatment.

Table 5. Effect of medical history (diseases) and previous hyperkalemic drug treatment on variation in serum potassium levels

	Variation of potassium in mEq/l (initial K) – (end K)		
	Presence of disease Mean (SD)	Absence of disease Mean (SD)	*p*
Hypertension (mean ± SD)	1.53 (0.64)	1.51 (0.69)	NS
Diabetes (mean ± SD)	1.48 (0.68)	1.54 (0.66)	NS
Heart disease	1.43 (0.56)	1.61 (0.75)	NS
Liver disease	1.63 (0.74)	1.49 (0.64)	NS
Chronic renal failure	1.47 (0.59)	1.53 (0.68)	NS
Nº of drugs			
0	1.42 (0.62)		NS
1	1.63 (0.76)		NS
2 or more	1.43 (0.49)		NS

End K: Potassium level at three hours after treatment; SD: standard deviation; NS: not significant.

salbutamol alone[4,5,9], the results of this study found no differences. This is consistent with the findings of Allon et al.[16] in their study of patients with renal failure on replacement therapy with dialysis who also found no difference between the two types of treatment. The discrepancies in potassium reduction between different studies are difficult to explain. Perhaps the number of patients included in the present study is insufficient to show significant differences between the two treatment regimes. Furthermore, all patients in our study responded to treatment. This conflicts with the results of some other studies, such as that by Allon et al,[16] but might be attributable to the small sample size of patients with chronic renal failure in our series.

Nebulized salbutamol usually achieves potassium reduction within 15-30 minutes of administration, is more effective at doses of 20 mg, and its effect is maintained for at least 2 hours[4]. Our study confirms this fact; we observed a decrease in plasma potassium three hours after the administration of salbutamol. The mechanism of action is stimulation of the Na-K ATPase pump, which induces potassium input into the cell[10]. This effect is transient, so the remaining treatment measures must be applied at the same time, such as hyperkalemic drug withdrawal, administration of ion exchange resins and the treatment of the cause of increased serum potassium.

The limitations of this study include the fact that it was performed in a single center. However, it included a fairly large number of patients and we therefore believe it provides valuable information. Another limitation is the difference in initial serum potassium between the two groups, but the results did not change due to this fact which suggests it probably had little or no influence. Finally, another limitation might be the use of salbutamol; although it has been shown to be effective even in preterm infants[17], paradoxical reactions have been observed in some patients when administered in nebulized form[18]. However, salbutamol is one of the most widely used forms of β_2 in our country and in the present study we found no such reaction in any case.

In summary, nebulized salbutamol alone showed similar efficacy to nebulized salbutamol with insulin plus glucose for the initial treatment of hyperkalemia, so we conclude it is a valid alternative without adverse effects.

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Estudio comparativo de salbutamol nebulizado en monoterapia o asociado a glucosa más insulina en el tratamiento de la hiperpotasemia

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Introducción: La hiperpotasemia es un trastorno potencialmente letal, que se detecta con relativa frecuencia en los servicios de urgencias. En su tratamiento se contemplan los beta$_2$-adrenérgicos junto a otros tratamientos. El objetivo de este estudio es comparar la eficacia del salbutamol nebulizado con la combinación de salbutamol nebulizado asociado a insulina más glucosa en el tratamiento de la hiperpotasemia.
Método: Estudio prospectivo y aleatorizado de los pacientes a los que se les detectó hiperpotasemia (K > 5,5 mEq/l). Se dividieron en dos grupos: monoterapia con salbutamol nebulizado o salbutamol nebulizado asociado a insulina más glucosa. Se añadió bicarbonato cuando existía alteración del equilibrio ácido-base. Se recogieron datos de filiación, antecedentes y medicación hipercalemiante. Se registró la reducción plasmática de potasio y el diagnóstico al alta. Se realizó una comparación entre grupos.
Resultados: Se incluyó a 81 pacientes (40 en el grupo monoterapia). La media de potasio inicial fue inferior en el grupo monoterapia [6,35 (0,4) *vs* 6,88 (0,7) mEq/l; p < 0,001]. En ambos grupos se observó una reducción significativa de los valores de potasio a las tres horas [1,41 (0,7) y 1,59 (0,6) mEq/l, respectivamente; ambos p < 0,001]. Este resultado fue independiente del potasio inicial. No existieron diferencias en la reducción de potasio entre ambos grupos. La reducción del potasio no se vio influenciada por los antecedentes ni por la administración de fármacos potencialmente hipercalemiantes.
Conclusiones: El salbutamol nebulizado en monoterapia tiene una eficacia similar al salbutamol nebulizado asociado a insulina más glucosa en el tratamiento de la hiperpotasemia. [Emergencias 2013;25:37-42]

Palabras clave: Hiperpotasemia. Tratamiento. Salbutanol nebulizado. Glucosa-insulina.