# Acute Therapy for Hyperkalemia with the Combined Regimen of Bicarbonate and Beta$_2$-adrenergic agonist (salbutamol) in Chronic Renal Failure Patients

This study was aimed to evaluate the efficacy of combination therapy of bicarbonate and salbutamol for hyperkalemia in 9 hemodialysis patients. Simultaneous administration of 8.4% sodium bicarbonate (i.v., 2 mEq/kg) for 1/2 hour and salbutamol (15 mg) in nebulized form for 10 min was compared with treatment modality of either bicarbonate or salbutamol alone. Infusion of sodium bicarbonate induced a significant rise in plasma bicarbonate from 17.3 ±3.2 to 22.1 ± 2.4 mEq/L ($p<0.01$), but was ineffective in lowering plasma potassium (- 0.13±0.06 mEq/L). As expected, salbutamol significantly lowered plasma potassium (- 0.57±0.03 mEq/L, $p<0.02$ vs. basal value) in all except 2 patients. The combined regimen of bicarbonate and salbutamol to a total 9 patients including 2 patients without hypokalemic effect to salbutamol alone revealed a substantially greater fall in plasma potassium (- 0.96 ±0.08 mEq/L, $p=0.000$ vs. either drug alone) accompanied with significant increase in plasma bicarbonate and blood pH. Treatment with salbutamol or the combined regimen produced slight increases in heart rate, but not in blood pressure. It is concluded that the combined regimen of bicarbonate and beta$_2$-adrenergic agonist (salbutamol) could be recommended as an efficient alternative for severe hyperkalemia in uremic patients, and is suggested that the enhanced transcellular hypokalemic effects of salbutamol in this combined regimen with bicarbonate would be related to the activation of Na-K pump with acute correction of underlying metabolic acidosis. *(JKMS 1997; 12 : 111~6)*

Key Words : *Treatment, Hyperkalemia, Bicarbonate, Salbutamol, Metabolic acidosis*

**Ho-Jung Kim**

Department of Internal Medicine,
Hanyang University Kuri Hospital,
Kuri, Korea

Received : October 24, 1996
Accepted : February 1, 1997

**Address for correspondence**
Ho-Jung Kim, MD.,
Department of Internal Medicine,
Hanyang University Kuri Hospital,
#249-1 Kyomoon-Dong, Kuri,
Kyunggi-Do 471-020, Korea.
Tel : (0346) 60-2230, Fax : (0346) 67-5666

## INTRODUCTION

Various therapeutic approaches to lower plasma potassium level in severe hyperkalemia of end-stage renal disease (ESRD) patients have been recommended for hyperkalemic emergencies (1~4). Of them, the definitive treatment of severe hyperkalemia in ESRD patients is to remove potassium from the body by dialysis, preferably hemodialysis. However, the initiation of dialysis is often delayed, especially at night or on weekend and other therapeutic approaches have been utilized as temporizing measures until dialysis becomes available.

After the serious cardiotoxic effects of hyperkalemia was antagonized by the intravenous administration of calcium salts, the most commonly utilized therapeutic approaches in a recent survey were intravenous administration of sodium bicarbonate and insulin with glucose (5). Also, the beta$_2$-adrenergic agonist such as albuterol or salbutamol, either in nebulized form or by intravenous route, have also been shown to have a potassium-lowering effect in hemodialysis patients (6, 7). However, clinical investigations in the past few years raised doubts about the utility of intravenous bicarbonate alone for the acute treatment of hyperkalemia (3, 8) while a new observation noticed the enhanced potassium-lowering effect of insulin with glucose by the simultaneous administration of bicarbonate as a combined therapy (9). Moreover, the addition of beta$_2$-adrenergic agonist (albuterol) to insulin with glucose as the combined therapy for hyperkalemia was shown to be efficacious and safe in a recent study (10).

To date, since it is unknown whether a similar synergism exists between bicarbonate and beta$_2$-adrenergic agonist (albuterol or salbutamol), the present study was undertaken to evaluate the potassium-lowering effect of the combined regimen of beta$_2$-adrenergic agonist (salbutamol) and intravenous bicarbonate, and to compare the effect with that of salbutamol in nebulized form alone and with that of bicarbonate alone in hyperkalemic ESRD patients.

## MATERIALS AND METHODS

Nine patients on maintenance hemodialysis with body weights between 55 and 65 kg and predialysis plasma potassium greater than 5.5 mEq/L on 3 consecutive measurements were recruited to the study after informed consent for participation had been obtained. No one had a history of diabetes mellitus nor had anyone received any medication interfering with potassium homeostasis such as beta-adrenergic blockers, angiotensin converting enzyme inhibitors or digitalis. The patients were 7 men and 2 women, with ages ranging from 38 to 63 years (mean±SE, 51.7±3.4 years).

Each subject was studied in three separate phases separated from one another by at least 1 week. The studies in each phase were performed in the recumbent position following an overnight fast immediately before a regularly scheduled hemodialysis. Indwelling venous catheters were placed into a radial arteriovenous fistula for repeated blood samplings. After obtaining a baseline blood sample, each subject received one of three treatments: (a) 8.4% sodium bicarbonate, 2 mEq/kg, given as an intravenous infusion over 30 minutes; (b) a nebulized treatment of salbutamol, 15 mg in 3 ml normal saline, inhaled over 10 minutes; or (c) a combined regimen consisting of intravenous bicarbonate plus nebulized salbutamol treatment.

Basal levels of plasma potassium and blood gas parameters were measured before and after treatment with one of the three experiments at 60 minutes. Blood pressure and pulse rates were measured at baseline and immediately before each blood sampling. All blood samples were collected in heparinized tubes, were centrifuged promptly, and were assayed for plasma potassium by flame photometry and blood gas analysis for pH and calculated bicarbonate concentrations with a blood gas analyzer (Corning 178, Corning Medical and Scientific, Mass., USA).

All values are expressed as mean ± SE. Statistical comparisons between the baseline and subsequent values were performed by analysis of variance and the paired Student's *t* test analysis. Differences within groups were analyzed by the Wilcoxon signed ranks test. A p value less than 0.05 was considered statistically significant.

## RESULTS

The mean basal plasma potassium concentrations were similar in all three experimental phases (5.96 to 5.99 mEq/L, see following).

As shown in table 1, during bicarbonate infusion alone, mean plasma potassium level was 5.98±0.24 mEq/L before and declined slightly to 5.84±0.34 mEq/L without significance. As expected, nebulized salbutamol alone produced a significant fall in plasma potassium from 5.99±0.30 to 5.42±0.50 mEq/L ($p<0.05$). The combined therapy with bicarbonate and nebulized salbutamol showed the most rapid decline in plasma potassium from 5.96±0.31 to 5.00±0.31 mEq/L ($p= 0.000$), a greater fall in plasma potassium than that with nebulized salbutamol alone. Following bicarbonate infusion, 5 of 9 study subjects (56%) showed an increase in plasma potassium concentrations from baseline values (Fig. 1, 2). Two patients (22%) seemed relatively resistant to the hypokalemic effect of nebulized salbutamol alone while all patients responded to the combined therapy with unanimous decline from baseline potassium levels, suggesting a greater intracellular shift of potassium by the simultaneous administration of bicarbonate (Fig. 1, 2). The individual change in plasma potassium ranged from 0.1 to -0.4 mEq/L (mean ± SE,

**Table 1.** Changes of plasma potassium, bicarbonate, and pH after 1 hour following intravenous infusion of bicarbonate, nebulized salbutamol, and in combination of them

| | Bicarbonate | Salbutamol | Bicarbonate + Salbutamol |
|---|---|---|---|
| K (mEq/L) | | | |
| Before | 5.98 ± 0.24 | 5.99 ± 0.30 | 5.96 ± 0.31 |
| After | 5.84 ± 0.34 | 5.42 ± 0.50 | 5.00 ± 0.31 |
| p | NS | < 0.05 | 0.000 |
| $HCO_3$ (mEq/L) | | | |
| Before | 20.3 ± 3.2 | 20.0 ± 2.1 | 21.0 ± 2.5 |
| After | 25.1 ± 2.4 | 21.2 ± 2.1 | 26.0 ± 2.4 |
| p | < 0.01 | NS | < 0.01 |
| pH | | | |
| Before | 7.33 ± 0.04 | 7.35 ± 0.02 | 7.34 ± 0.03 |
| After | 7.41 ± 0.03 | 7.36 ± 0.03 | 7.42 ± 0.04 |
| p | < 0.01 | NS | < 0.01 |

NS = not significant

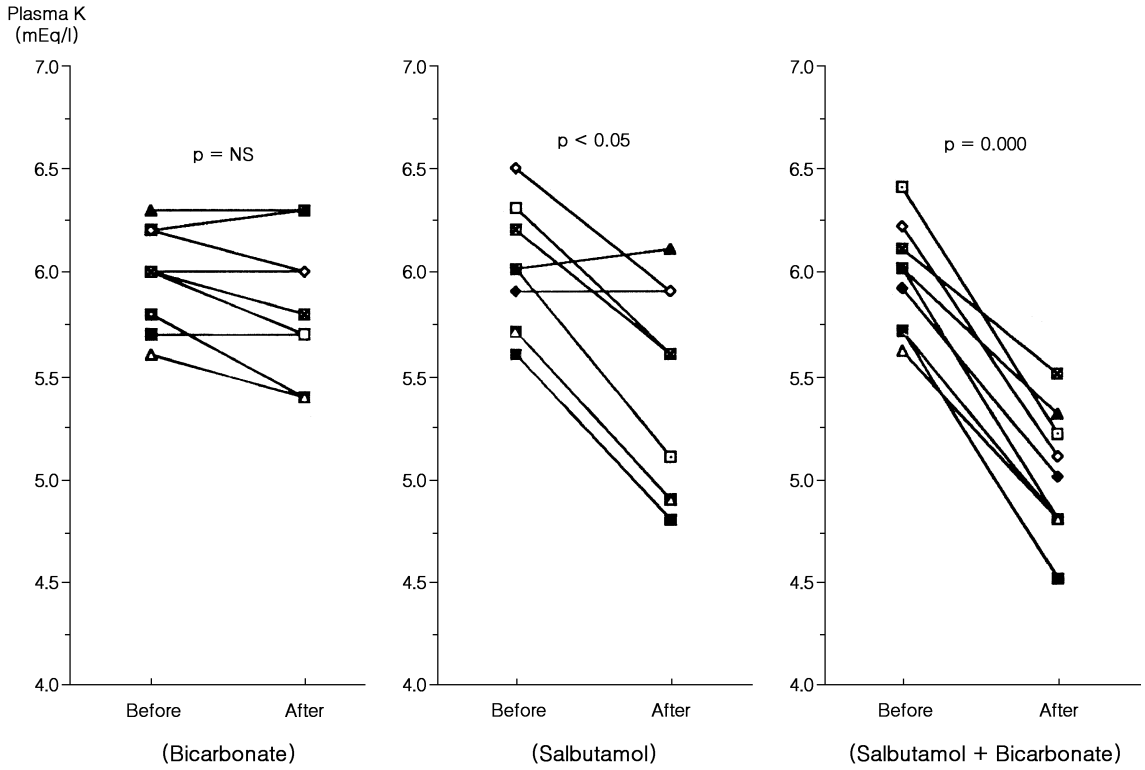


**Fig. 1.** Changes in plasma potassium of individual study subjects(n=9) following intravenous infusion of bicarbonate, nebulized salbutamol, and in combination of them.

-0.13 ± 0.06 mEq/L) after bicarbonate, 0.1 to -0.9 mEq/L (mean ± SE, -0.57 ± 0.12 mEq/L) after nebulized salbutamol alone, and -0.6 to -1.2 mEq/L (mean ± SE, -0.96 ± 0.08 mEq/L ) after the combined therapy, respectively (Fig. 2).

The basal plasma bicarbonate concentrations and pHs were lower than normal, indicating the presence of mild metabolic acidosis, and were similar in all three experimental phases (Table 1). The plasma bicarbonate concentration increased from 20.3±3.2 to 25.1±2.4 mEq/L with infusion of bicarbonate alone, and from 21.0±2.5 to 26.0±2.4 mEq/L with combined treatment of bicarbonate plus nebulized salbutamol. Simultaneously, the blood pH rose from 7.33±0.04 to 7.41±0.03 ($p<0.01$) with bicarbonate alone, and from 7.34±0.03 to 7.42±0.04 ($p<0.01$) with the combined treatment. The administration of nebulized salbutamol did not show any significant changes from basal values in plasma bicarbonate and pH (Table 1).

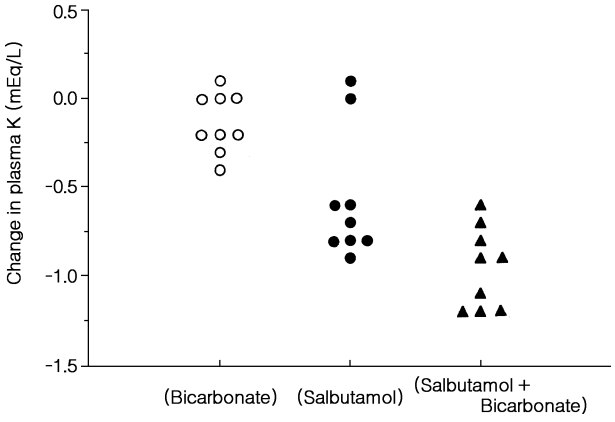


**Fig. 2.** Individual change of plasma potassium from baseline value following intravenous infusion of bicarbonate, nebulized salbutamol, and in combination of them.

As shown in table 2, the baseline mean blood pressures as well as the baseline heart rates before the administration of nebulized salbutamol alone or nebulized salbutamol plus bicarbonate infusion were not significantly different. After treatments, the heart rate rose mildly from 78±5 to 92±3/min with nebulized salbutamol alone ($p<0.05$) and from 81±2 to 93±2 /min with the combined treatment ($p<0.05$), whereas the blood pressure following both regimens did not show any significant changes. Moreover, no one of the 9 study subjects complained of tremor, palpitation or chest pain after the administration of either nebulized salbutamol alone or nebulized salbutamol plus bicarbonate.

**Table 2.** Clinical parameters before and after nebulized salbutamol or combined treatment with nebulized salbutamol and bicarbonate

| Parameters | Before treatment | After treatment | p |
|---|---|---|---|
| Heart rate (beats/min) | | | |
| Salbutamol | 78 ± 5 | 92 ± 3 | < 0.05 |
| Salbutamol + Bicarbonate | 81 ± 2 | 93 ± 2 | < 0.05 |
| Blood pressure (mmHg) | | | |
| Salbutamol | 153 ± 4 / 84 ± 5 | 151 ± 4 / 82 ± 5 | NS |
| Salbutamol + Bicarbonate | 150 ± 3 / 81 ± 4 | 148 ± 4 / 80 ± 5 | NS |

## DISCUSSION

Despite close monitoring and repeated dietary counseling, the patients with advanced renal failure and on maintenance hemodialysis are at a high risk for life-threatening hyperkalemia, which is associated with high mortality rates itself or is often accompanied with cardiac arrest of unknown cause (11~13).

Based on these considerations, various therapeutic approaches have been developed for acute therapy of hyperkalemia in patients on chronic dialysis. Besides the reversal or removal of the specific aggravating causes of the hyperkalemia such as dietary potassium excess, fasting, and drugs including beta-adrenergic blockers or angiotensin converting enzyme inhibitors (2), the acute therapy of hyperkalemia described in the standard medical or nephrology textbooks or in the recent reviews of management of hyperkalemia can be divided into three general categories (2, 4, 14) : 1) to oppose the direct toxic effects of hyperkalemia on the cell membrane with calcium salts ; 2) to promote cellular uptake of potassium by sodium bicarbonate, insulin with glucose, or $beta_2$-adrenergic agonists ; and 3) to remove potassium from the body with diuretics, cation-exchange resins, or dialysis.

Among these approaches, infusion of calcium salts was chosen as the preferred initial treatment for severe hyperkalemia in ESRD for the efficient and rapid antagonizing effect of serious cardiac toxicity of hyperkalemia (5), but the effect is quite transient because it neither lowers plasma potassium nor removes potassium from the body. Moreover, there are certain limitations in selecting the above therapeutic options for ESRD patients on dialysis. For example, diuretics can do little to enhance renal potassium excretion in virtually anephric ESRD patients. Cation-exchange resins (e.g. Kayexalate) have a relatively slow onset of action, 1~2 hours, which limits their usefulness in the acute therapy of severe hyperkalemia. Undoubtedly, the emergent hemodialysis is the most effective and definitive method for the removal of excess potassium, but the initiation of hemodialysis often involves 1 to 2 hours delay, and is often unavailable at night and on weekend. Hence, there is a need for other temporizing measures useful for the acute treatment of hyperkalemia prior to initiation of hemodialysis.

After the myocardium is stabilized with intravenous calcium salts, the temporizing measures directed at decreasing plasma potassium acutely by the transcellular shift are often used prior to initiation of hemodialysis. These measures include 3 principal modalities including intravenous sodium bicarbonate, insulin with glucose, and $beta_2$-adrenergic agonists (albuterol or salbutamol) in nebulized form or intravenous route. Most of the previous observations have been made on the individual effect of these three basic modalities as mono-therapy, but recently two studies introduced the efficacious and safe modalities for the acute treatment of hyperkalemia in ESRD patients with the combined regimens as dual-therapy. Those combined regimens are insulin with glucose plus $beta_2$-adrenergic agonist (albuterol), and bicarbonate plus insulin with glucose (9, 10), but not dual-therapy of bicarbonate plus $beta_2$-adrenergic agonist. Therefore, the main aim of this study was to compare the potassium-lowering effect of the combined regimen with bicarbonate and $beta_2$-adrenergic agnonist using salbutamol, to that of either regimen alone.

Despite the widely held view in the standard nephrology and electrolyte textbooks that sodium bicarbonate is effective in lowering plasma potassium, several prospective clinical studies showed no change in plasma potassium during one hour of administration of bicarbonate to hemodialysis patients, and questioned its usefulness for the acute therapy of hyperkalemia in ESRD patients (3, 8, 9). Also, in the current study, intravenous infusion for 1 hour failed to lower plasma potassium in ESRD patients. Therefore, the role of intravenous bicarbonate alone as a mono-therapy for acute therapy of hyperkalemia in ESRD patients remains questionable until further clarification.

Our data confirmed the previous observations that $beta_2$-adrenergic agonists are effective in reducing plasma potassium rapidly and reliably. $Beta_2$-adrenergic agonists translocate potassium intracellularly by activation of the

Na-K pump but by different cellular mechanisms from hypokalemic effect of insulin (15). Beta$_2$-adrenergic agonists activate Na-K ATPase by stimulating cyclic adenosine triphosphate (cAMP) as a second messenger. Therefore, we can speculate that this activation of the Na-K pump would somehow enhance the hypokalemic effect of beta$_2$-adrenergic agonist. For example, the combined therapy of albuterol plus insulin with glucose has shown to cause a substantially greater decrease in plasma potassium than each drug alone (10).

In the present study, bicarbonate alone had little effect on plasma potassium, but it enhanced the hypokalemic effect of nebulized salbutamol ; the combination therapy reduced plasma potassium much more than nebulized salbutamol alone ($0.57 \pm 0.03$ vs. $0.96 \pm 0.08$ mEq/L. $p = 0.000$, Fig. 2). Furthermore, 2 of 9 study patients were refractory to the potassium-lowering effect of nebulized salbutamol alone as noticed in a subset of ESRD patients of the previous study (6, 7), but which was corrected by the simultaneous administration of intravenous bicarbonate in the combined regimen (Fig. 1).

Chronic renal failure is associated with an impairment of Na-K pump activity. The etiology of the defect in Na-K pump in uremia is poorly characterized. Among many factors the presence of metabolic acidosis was proposed in addition to other factors such as fluid overload, endogenous ouabain-like substance, thyroxine deficiency, and hyperparathyroidism (16). Significant increases in blood pH and plasma bicarbonate were noted with the administration of bicarbonate alone or with that of bicarbonate plus nebulized salbutamol in the combined regimen. Therefore, the hypokalemic effect of nebulized salbutamol enhanced by the addition of bicarbonate might be related to alkalinization, perhaps through the activation of the Na-K pump. The hypokalemic effect of nebulized salbutamol through the activation of Na-K pump by Na-K ATPase could be driven by increased Na entry with the activation of Na/H ion antiporter like insulin as shown in an animal study, which was further enhanced by alkalemia with increased H ion efflux from ECF when bicarbonate was administered simultaneously (17).

Despite beta$_2$ selectivity, beta$_2$-adrenergic agonists still could cause adverse cardiovascular effects, particularly after intravenous administration (7). But, there was no other significant adverse cardiovascular side effects except tachycardia in this study. This indicates that administration of beta$_2$-adrenergic agonist in nebulized form may be safer than the intravenous route, especially in patients with underlying atherosclerotic heart disease.

In conclusion, this data in some respect confirm the previous findings: nebulized salbutamol alone is one of the effective modalities for acute therapy of hyperkalemia in ESRD patients as a temporizing measure, but bicarbonate alone is not. A new observation is that bicarbonate enhances the potassium-lowering effect of nebulized salbutamol with partial correction of underlying metabolic acidosis in ESRD patients. Hereby, the combined regimen of nebulized salbutamol and bicarbonate can be proposed as an effective and safe modality for the acute therapy of hyperkalemia in ESRD patients as previously reported regimens such as bicarbonate and insulin or insulin and nebulized albuterol.

## REFERENCES


1. Allon M. *Treatment and prevention of hyperkalemia in end-stage renal disease. Kidney Int 1993 ; 43 : 1197-209.*
2. Allon M. *Hyperkalemia in end-stage renal disease : mechanisms and management. J Am Soc Nephrol 1995 ; 6 : 1134-41.*
3. Blumberg A, Weidmann P, Ferrari P. *Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. Kidney Int 1992 ; 41 : 369-74.*
4. DeFronzo RA, Smith JD. *Clinical disorders of hyperkalemia. In: Narins RG, ed. Clinical Disorders of Fluid and Electrolyte Metabolism, 5th ed. New York : McGraw-Hill, 1994 ; 697-754.*
5. Iqbal Z, Friedman EA. *Preferred therapy of hyperkalemia in renal insufficiency : Survey of nephrology training-program directors. N Engl J Med 1989 ; 320 : 60-1.*
6. Allon M, Dunlay R, Copkney C. *Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. Ann Int Med 1989 ; 110 : 426-9.*
7. Liou HH, Chiang SS, Wu SC, Huang TP, Campese VM, Smogorzewski M, Yang WC. *Hypokalemic effects of intravenous infusion or nebulization of salbutamol in patients with chronic renal failure : Comparative study. Am J Kid Dis 1994 ; 23 : 266-71.*
8. Blumberg A, Weidmann P, Shaw S, Gnadinger M. *Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. Am J Med 1988 ; 85 : 507-12.*
9. Kim HJ. *Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. Nephron 1996 ; 72 : 476-82.*
10. Allon M, Copkney C. *Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. Kidney Int 1990 ; 38 : 869-72.*
11. Brynger H, Brunner FP, Chantler C, Donckerwolcke RA, Jacobs C, Kramer P, Selwood NH, Wing A. Combined report on regular dialysis and transplantation in Europe. *Proc Eur Dial Transplant Assoc 1980 ; 17 : 4-86.*
12. Siddiqui JY, Fitz AE, Lawton RL, Kirkendall WH. *Causes of death in patients receiving long term hemodialysis. JAMA 1970 ; 212 : 1350-4.*
13. Tzamaloukas AH, Avasthi PS. *Temporal profile of serum potassium concentration in nondiabetic and diabetic outpatients*

*on chronic dialysis. Am J Nephrol 1987; 7 : 101-9.*

14. Barr G, DeFronzo RA. *Treatment of hyperkalemia. In : Glassock RJ, ed. Current therapy in nephrology and hypertension, Vol 3. Philadelphia : Decker, 1991; 84-96.*
15. Clausen T, Flatman J. *The effect of catecholamines on Na-K transport and membrane potential in rat soleus muscle. J Physio (Lond) 1977; 270 : 383-414.*
16. Deepak K, Kahn T. *Na-K pump in chronic renal failure. Am J Physiol 1987; F785-F793.*
17. Goguen JM, Halperin ML. *Can insulin administration cause an acute metabolic acidosis in vivo? An experimental study in dogs. Diabetologia 1993; 36 : 813-6.*