

Oral Sodium Bicarbonate for the Treatment of Metabolic Acidosis in Peritoneal Dialysis Patients: A Randomized Placebo-Control Trial

CHEUK-CHUN SZETO, TERESA YUK-HWA WONG, KAI-MING CHOW, CHI-BON LEUNG, and PHILIP KAM-TAO LI

Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China.

Abstract. Acidosis causes malnutrition in peritoneal dialysis (PD) patients. The effect of oral bicarbonate in PD patients with $Kt/V < 2.1$ has not been studied. We randomly assigned 60 PD patients with acidosis and $Kt/V < 2.1$ to oral sodium bicarbonate (0.9 g thrice daily) or placebo. Patients were followed for 12 mo. We compared their nutritional status, including subjective global assessment (SGA) score and normalized protein nitrogen appearance (NPNA), hospitalization and all-cause mortality. Treatment with oral bicarbonate resulted in a higher plasma bicarbonate level at 4 wk (27.8 ± 2.6 versus 24.7 ± 3.9 mmol/L, $P = 0.002$), and the difference persisted until 52 wk. Bicarbonate treatment had a significant effect on the change in overall SGA score (repeated measures ANOVA,

$P = 0.0003$). The overall SGA score of the treatment group was higher than the placebo group at 24 wk (5.07 ± 0.94 versus 4.40 ± 1.00 , $P = 0.015$), and the difference persisted thereafter. NPNA rose in the treatment group (1.17 ± 0.32 to 1.28 ± 0.26 g/kg per d, $P = 0.034$), but declined in placebo group (1.13 ± 0.25 to 1.03 ± 0.28 g/kg per d, $P = 0.054$). The treatment group had a shorter hospitalization than the placebo group (8.4 ± 17.7 versus 16.8 ± 21.7 d/yr; $P = 0.02$). Mortality was not significantly different. Although our trial has limited statistical power, we find that in PD patients with mild acidosis and $Kt/V < 2.1$, oral sodium bicarbonate probably improve nutritional status and reduce the duration of hospitalization.

Malnutrition is common in renal failure patients and is associated with increased morbidity and mortality (1). In continuous ambulatory peritoneal dialysis (CAPD) patients, dialysis adequacy is important for satisfactory nutrition. For example, the CANUSA study has shown that a higher Kt/V is associated with higher lean body mass and subjective global assessment (SGA) score (2). However, it remains disputable whether increasing the dosage of peritoneal dialysis could improve nutritional status (3,4) or clinical outcome (5); many renal failure patients have progressive wasting and malnutrition despite apparently adequate dialysis (6).

Persistent acidosis is a major factor of malnutrition in renal failure patients (7,8). Although correction of acidosis by high-lactate dialysate improved the nutritional status and reduced the hospitalization of CAPD patients (9), extensive use of a high-lactate dialysate resulted in alkalosis in some patients (10), and the lactate concentration in dialysate cannot be adjusted according to need. Theoretically, oral sodium bicarbon-

ate is a convenient alternative because the dosage can be easily tailored. Nevertheless, the effect of oral sodium bicarbonate has not been extensively studied. In a small pilot study, it was effective in improving the nutritional status of CAPD patients with Kt/V of 2.1 (11). However, the effect of bicarbonate supplement in CAPD patients with $Kt/V < 2.1$ has not been studied. It is important to note that although a weekly Kt/V of 2.1 was often regarded as the target of dialysis adequacy (12), we found that Chinese CAPD patients with a Kt/V of 1.7 had excellent outcome (13). The ADEMEX study further showed that increases in peritoneal Kt/V from 1.62 to 2.13 had no effect on patient survival (5). It is therefore important to identify measures to improve the outcome of CAPD patients with Kt/V between 1.7 and 2.1. Here we report a randomized placebo-control study that evaluates the effects of correcting acidosis by oral sodium bicarbonate in CAPD patients with weekly $Kt/V < 2.1$.

Materials and Methods

Patient Selection

The study was approved by the Clinical Research Ethical Committee of the Chinese University of Hong Kong. Within 3 mo before randomization, plasma bicarbonate level was measured twice to determine eligibility for the trial. We screened 247 patients in our dialysis unit; 78 (31.6%) fulfilled the enrollment criteria. Based on the estimated sample size required (see below), we invited 60 patients to participate in the study. Recruitment criteria were: (1) total weekly Kt/V below 2.1; (2) venous bicarbonate ≤ 25 mmol/L on two consecutive measurements; and (3) stable clinical condition and CAPD

Received January 3, 2003. Accepted April 19, 2003.

Correspondence to Dr. C.C. Szeto, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China. Phone: 852-2632-3173; Fax: 852-2637-3852; E-mail: ccszeto@cuhk.edu.hk

1046-6673/1408-2119

Journal of the American Society of Nephrology

Copyright © 2003 by the American Society of Nephrology

DOI: 10.1097/01.ASN.0000080316.37254.7A

regimen for at least 12 mo. The recruited patients had $Kt/V < 2.1$ because of low exchange volume (42 patients had three 2-L exchange per day) or low/low-average peritoneal transporter. We excluded patients who were unlikely to survive or who planned to have elective living-related kidney transplant or transfer to other renal center within 6 mo.

After obtaining informed consent and initial evaluation, patients were randomized to receive either oral sodium bicarbonate 0.9 g thrice daily, or placebo (pure starch tablet), for 12 mo. The appearance, packaging, and labeling of the tablets were identical. Both kinds of tablets had artificial mint flavor to give an identical taste. Individuals were randomized by a computer-generated list, which was used for packaging of the tablets and then maintained by a third party that was not involved in the conduction of the study. Marked tablet packs were designated for each patient. Both patients and investigators were blinded. Results of biochemical analyses and nutritional assessments were completed before the randomization code was broken at the end of the study.

Clinical Follow-Up

Baseline clinical data were recorded by chart review. These included age, gender, underlying renal disease, CAPD regimen, duration on dialysis, and number and duration of hospitalization within 12 mo before recruitment. A panel of comorbid conditions, including coronary artery disease, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, liver disease, diabetes with and without complications, hemiplegia, malignancy, and AIDS, were also recorded. The modified Charlson Comorbidity Index, which was validated in CAPD patients (14), was used to calculate a comorbidity score.

Patients were followed at -4 , 0, 4, 12, 24, 36 and 52 wk. Except for the study medication, the clinical management was the same as in other patients. All patients were treated with conventional dextrose-based peritoneal dialysis solution with a lactate concentration of 35 mmol/L and calcium 1.25 mmol/L. No patient had amino acid or glucose polymer-based peritoneal dialysis solution. Dialysis prescription was changed only when there was clinical evidence of underdialysis (13). We documented the following during each follow-up visit: body weight, BP, presence of edema (semiquantitative score from 0 to 3+), drug compliance by pill count, and compliance to dialysis exchange by direct questioning. Hemoglobin level, venous bicarbonate, serum electrolytes, urea, and creatinine were checked on each clinic visit. At 0 wk, serum C-reactive protein (CRP) and fibrinogen levels were checked as baseline. CRP was measured by the Tina-quant CRP (Latex) ultra-sensitive assay (Roche Diagnostics, Mannheim, Germany), and fibrinogen by a prothrombin time-derived and turbidimetric clot detection method using the ACL Futura (Instrumentation Laboratory, Lexington, MA).

Nutritional Assessment

Nutritional status was assessed by subjective global assessment (SGA), normalized protein nitrogen appearance (NPNA), serum albumin level, anthropometric lean body mass (LBM), and fat-free edema-free body mass (FEBM). SGA was performed at 0, 12, 24, 36, and 52 wk by two trained observers who were blinded from the treatment group allocation and biochemical results of the patients. The four-item seven-point system was used (12,15). The four items for assessment were change in body weight, the degree of anorexia, and the amount of subcutaneous tissue and muscle mass. The four individual item scores were then combined to generate a global score,

which also took into account the clinical judgment of the observers and thus did not represent the simple arithmetic aggregate of the four individual item scores. All SGA items were rated subjectively on a scale of 1 to 7, where 1 or 2 is severe malnutrition, 3 to 5 is moderate to mild malnutrition, and 6 or 7 is mild malnutrition to normal nutritional status (12). Before the start of this study, the two observers were trained to achieve a Cohen's kappa concordant coefficient for agreement of 0.84, which was an excellent level of agreement. Anthropometric measurements were performed at 0, 12, 24, 36, and 52 wk by two trained observers. The measurements included biceps, triceps, subscapular and supra-iliac skin-fold thickness. Anthropometric LBM was computed with the formula described by Durnin and Rahaman (16). The interobserver coefficient of variation of LBM was around 10%.

At 0, 24, and 52 wk, 24-h urine and dialysate collection was performed. FEBM was calculated according to the formula described by Forbes and Brunining (17). NPNA was calculated by the modified Bergstrom's formula (18) and normalized by the ideal body weight (IBW), which was determined by the body height and gender according to a standard formula validated in Southern Chinese (19). Kt/V and weekly creatinine clearance (CCr) were determined by standard methods (20). Residual GFR was calculated as average of 24 h urinary urea and creatinine clearance as described (21). Serum albumin was measured by bromocresol purple method. All biochemical tests were performed in our hospital laboratory, which has meticulous quality control and is accredited as the Area of Medical Testing by the National Association of Testing Authorities (NATA), Australia, in conjunction with the Royal College of Pathologists of Australasia.

The primary outcome measure was the SGA score. Secondary outcomes included the total number and total duration of hospital admission during the study period, other nutritional indices as detailed above, technique failure and all-cause mortality. Technique failure was defined as transfer to long-term hemodialysis.

Statistical Analyses

The sample size was estimated before the study by the Power Analysis and Sample Size for Windows software (PASS 2000; NCSS, Kaysville, UT), with the SGA as the primary outcome measure. Because the CANUSA study found that a difference in SGA score of 1 was clinically relevant (2), and preliminary data showed that the SD of SGA score was 1.3, use of sample sizes of 60 achieves 81% power to detect a difference of 1.0 between the groups and with a significance level (α) of 0.05.

Statistical analysis was performed by SYSTAT 7.0 software (SPSS, Chicago, IL). All data were expressed as mean \pm SD unless otherwise specified. A P value of less than 0.05 was considered statistically significant. All probabilities were two tailed. Analyses were intention to treat irrespective of adherence to treatment regimen. Data between treatment groups were compared by χ^2 test, t test, or Kruskal-Wallis test, as appropriate.

To analyze the effect of sodium bicarbonate on longitudinal changes in nutritional indices, repeated measures ANOVA was used, with the nutritional indices (for example, SGA score) as the repeated measure, treatment group as the between-group factor, and the Charlson Comorbidity Index as covariate. In this model, longitudinal change of a variable is represented by the interactions between follow-up time and the variable. A significant interaction between the treatment group and time indicates treatment group allocation has a significant effect on the parameter. Post hoc analysis was performed by t test with Bonferroni's adjustment. The number and duration of hospital admission was compared between groups by analysis of

covariance (ANCOVA). In this analysis, hospitalization data were used as dependent variable (after correction for the duration of follow-up and log-transformation because the data were highly skewed), treatment allocation was used as grouping factor, and the Charlson Comorbidity Index as the covariate. Actuarial patient survival was compared by log rank test.

Results

The baseline clinical characteristics, major comorbid conditions, and markers of systemic inflammation are shown in Table 1. Dialysis adequacy indices and residual GFR are shown in Table 2. There was no significant difference in any baseline parameter between the two groups. Although the treatment group had marginally more patients with underlying heart failure and fewer patients with cerebrovascular disease than the control group, the differences were not statistically significant. The average BP throughout the study was 144/78 mmHg in the treatment group, and 143/81 mmHg in the control group ($P = 0.79$ for the comparison of mean BP). There was no difference in the number of anti-hypertensive medications between the two groups. There were 21 patients in the treatment group, and 20 in the control group, who received calcium carbonate as phosphate binder. The average dose of calcium carbonate was 2.25 ± 1.70 and 2.55 ± 2.20 g per day, respectively ($P = 0.6$).

Four patients in the treatment group could not tolerate the study medication because of dyspepsia (3 cases) or dizziness (1 case). Study medication was stopped in 3 patients of the placebo group because of dyspepsia (2 cases) or skin rash (1 case). Although study medication was stopped in these patients, biochemical tests and nutritional assessment were continued for 52 wk according to the study protocol. Compliance of the other patients was over 90% by pill count.

Biochemistry

Venous plasma bicarbonate levels during the study period are summarized in Figure 1. In the placebo group, there was a small but statistically significant rise in plasma bicarbonate level from 22.8 ± 1.7 to 24.7 ± 3.9 mmol/L at 4 wk ($P = 0.01$). In the treatment group, plasma bicarbonate level rose from 22.9 ± 1.6 to 27.8 ± 2.6 mmol/L after 12 wk ($P < 0.0001$). Although plasma bicarbonate level of the treatment group gradually declined during the study period, it remained significantly higher than that of the placebo group at all time points.

In the treatment group, there was a small but statistically significant rise in serum sodium level from 137.1 ± 2.2 to 139.4 ± 2.5 mmol/L ($P = 0.0001$), and a small decline in serum potassium level from 4.37 ± 0.65 to 4.04 ± 0.74 mmol/L ($P = 0.03$) after 4 wk, and both remained stable thereafter. Serum sodium and potassium levels remained static in the placebo group.

Nutritional Status

The edema and SGA scores are summarized in Figure 2 and Table 3. The edema scores of the two groups remained similar between the groups. In the treatment group, overall SGA score

Table 1. Baseline characteristics of the patients

	Placebo Group	Treatment Group
No. of patient	30	30
Gender (M:F)	19:11	16:14
Age (yr)	56.6 ± 13.2	54.3 ± 12.4
Duration of dialysis (mo)	39.4 ± 26.0	39.9 ± 20.8
Body height (m)	1.59 ± 0.07	1.61 ± 0.08
Body weight (kg)	63.2 ± 11.1	62.9 ± 8.7
Mean BP (mmHg)	103.3 ± 11.2	100.5 ± 10.9
Diagnosis (no. of cases)		
glomerulonephritis	11	11
diabetes	8	12
polycystic	3	0
obstruction	2	2
others/unknown	6	5
Major comorbidity (no. of cases)		
coronary heart disease	7	6
congestive heart failure	8	12
peripheral vascular disease	2	2
cerebrovascular disease	6	1
dementia	0	0
chronic pulmonary disease	1	1
connective tissue disorder	0	1
peptic ulcer disease	2	7
mild liver disease	2	1
diabetes	1	0
hemiplegia	0	0
moderate or severe renal disease	30	30
diabetes with end-organ damage	8	12
any tumour, leukemia, lymphoma	0	1
moderate or severe liver disease	0	1
metastatic solid tumour	0	0
AIDS	0	0
Charlson Index score	4.8 ± 1.8	5.3 ± 2.0
Daily exchange volume		
6-L	19	23
8-L	11	7
Serum CRP (mg/L) ^a	3.23 ± 3.70	3.64 ± 5.32
Fibrinogen level (g/L) ^b	7.10 ± 2.85	6.55 ± 1.26

^a CRP, C-reactive protein (normal < 9.9 mg/L); ^b Normal range of fibrinogen, 1.97–3.63 g/L.

Table 2. Dialysis adequacy and residual renal function^a

	0 wk	24 wk	52 wk
Total Kt/V			
treatment group	1.91 ± 0.52	1.90 ± 0.61	1.77 ± 0.31
placebo group	1.93 ± 0.51	1.86 ± 0.40	1.78 ± 0.30
Dialysate protein loss (g/d)			
treatment group	6.4 ± 2.5	6.2 ± 2.5	6.2 ± 2.1
placebo group	6.6 ± 2.6	6.2 ± 3.8	6.8 ± 3.9
Residual GFR (ml/min)			
treatment group	1.78 ± 2.36	1.29 ± 2.13	0.81 ± 1.04
placebo group	1.91 ± 2.65	1.14 ± 1.78	0.68 ± 1.04
Proteinuria (g/d)			
treatment group	0.74 ± 2.03	0.19 ± 0.32	0.16 ± 0.57
placebo group	0.51 ± 0.64	0.30 ± 0.52	0.25 ± 0.41

^a CCr, creatinine clearance rate; GFR, glomerular filtration rate.

Note: There was no statistically significant difference between groups.

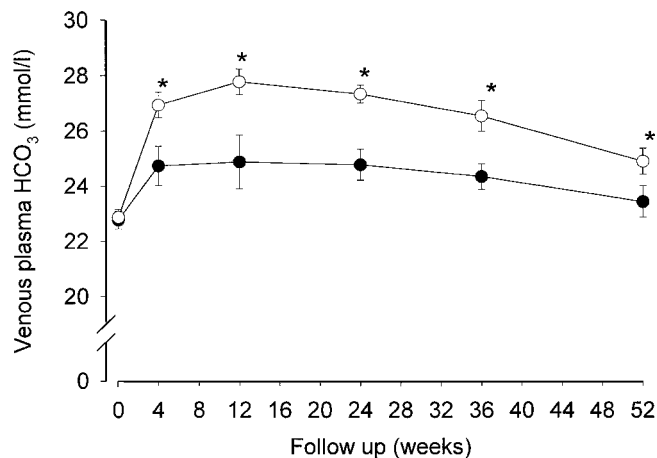


Figure 1. Venous plasma bicarbonate levels (mmol/L) in treatment group (open circles) and placebo group (closed circles). Error bars denote SEM. * $P < 0.01$ between treatment and placebo groups.

rose from 0 to 24 wk and then became stabilized, whereas that of the placebo group remained static. Repeated measure ANOVA showed that there was a significant effect of bicarbonate treatment on the change in overall SGA score ($P = 0.0003$). Post hoc analysis showed that treatment group had higher overall SGA score than the placebo group at 24 wk (5.07 ± 0.94 versus 4.40 ± 1.00 , $P = 0.015$), and the difference persisted until 52 wk. When the four-item SGA scores were analyzed (Table 3), similar trends were observed in all items, although only the changes in the scores of anorexia and weight loss were statistically significant. There was no significant change in the actual body weight of the two groups (details not shown).

After adjusting for Charlson Comorbidity Index, there was a significant effect of bicarbonate treatment on the change in NPNA (repeated measure ANOVA, $P = 0.045$). Post hoc

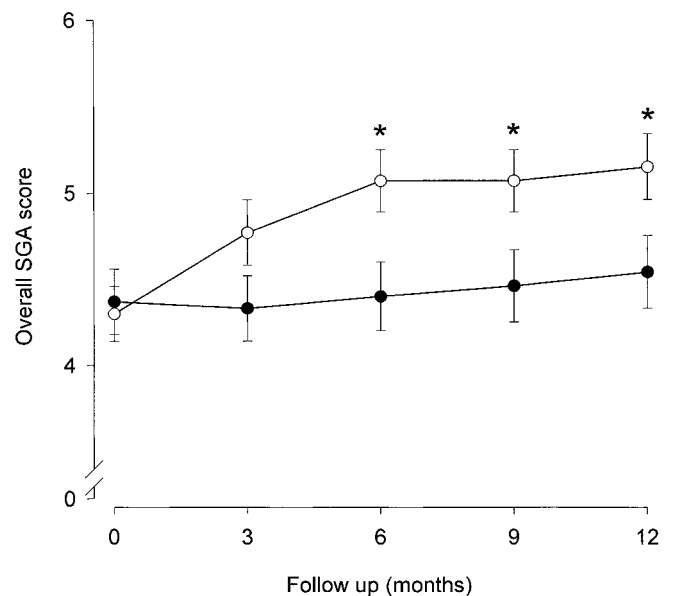


Figure 2. Overall subjective global assessment (SGA) score at baseline and follow-up of patients on the treatment group (open circles) or the control group (closed circles). There was no significant difference between the groups at baseline. Error bar denotes SEM. * $P < 0.05$ between treatment and control groups.

analysis showed that NPNA rose from 1.17 ± 0.32 to 1.28 ± 0.26 g/kg per d in the treatment group ($P = 0.034$), but declined from 1.13 ± 0.25 to 1.03 ± 0.28 g/kg per d ($P = 0.054$) in the placebo group, although the latter was not statistically significant (Figure 3).

During the study period, FEBM of the treatment group rose from 0 to 24 wk (30.8 ± 8.4 to 34.3 ± 10.9 kg, $P = 0.04$) and then became stabilized (Figure 3). FEBM remained static in the placebo group. The anthropometric LBM remained stable in the treatment group (Figure 3), but declined significantly in the placebo group from 0 to 12 wk (50.7 ± 7.0 to 48.9 ± 7.1 kg, $P = 0.002$). However, the overall differences in FEBM and anthropometric LBM between the groups were not statistically significant after adjusting for the Charlson Comorbidity Index (repeated measures ANOVA, $P = 0.07$ and $P = 0.1$, respectively). Serum albumin level of the treatment group rose from 27.7 ± 4.3 to 28.9 ± 4.6 mmol/L after 4 wk ($P = 0.03$) but returned to pretreatment level by 24 wk (Figure 3). Serum albumin level of the placebo group remained static. The difference in serum albumin level between the two groups was NS (repeated measures ANOVA, $P = 0.6$).

Hospitalization

The number of hospital admission and duration of hospitalization are summarized in Table 4. The frequency distribution of hospitalization duration is summarized in Figure 4. Although study medication was stopped prematurely in 7 patients, their data on hospitalization were collected until 52 wk. After adjusting for the Charlson Comorbidity Index score, the treatment group had marginally fewer hospital admissions (1.8 ± 3.1 versus 2.4 ± 2.8 per year, $P = 0.07$), which was not

Table 3. Edema and subjective global assessment (SGA) scores

	0 wk	12 wk	24 wk	36 wk	52 wk	<i>P</i> value ^a
Edema						0.7
treatment group	1.03 ± 0.72	0.70 ± 0.92	0.46 ± 0.84	0.63 ± 0.84	0.46 ± 0.65	
placebo group	1.00 ± 0.87	0.80 ± 0.71	0.56 ± 0.82	0.58 ± 0.83	0.75 ± 1.03	
Overall SGA score						0.0003
treatment group	4.30 ± 0.88	4.77 ± 1.04	5.07 ± 0.94	5.07 ± 0.96	5.15 ± 0.97	
placebo group	4.37 ± 1.03	4.33 ± 1.03	4.40 ± 1.00	4.46 ± 1.02	4.54 ± 1.02	
Anorexia						0.0008
treatment group	4.33 ± 0.96	4.67 ± 1.09	4.96 ± 0.92	5.00 ± 1.04	5.15 ± 0.92	
placebo group	4.20 ± 1.24	4.40 ± 1.10	4.24 ± 0.88	4.46 ± 0.93	4.46 ± 1.02	
Weight loss						0.013
treatment group	4.40 ± 1.00	4.70 ± 1.06	5.11 ± 0.92	4.96 ± 1.19	5.19 ± 0.98	
placebo group	4.23 ± 1.14	4.30 ± 1.02	4.28 ± 0.84	4.54 ± 1.02	4.46 ± 0.98	
Subcutaneous fat						0.38
treatment group	4.47 ± 1.04	4.70 ± 1.12	4.82 ± 1.06	5.00 ± 1.07	5.11 ± 1.18	
placebo group	4.43 ± 1.14	4.40 ± 1.04	4.52 ± 0.92	4.71 ± 1.08	4.71 ± 1.04	
Muscle mass						0.18
treatment group	4.53 ± 0.94	4.73 ± 1.20	5.00 ± 1.09	4.96 ± 1.16	5.04 ± 1.28	
placebo group	4.33 ± 0.92	4.37 ± 1.03	4.36 ± 0.95	4.38 ± 1.06	4.54 ± 0.98	

^a Data are analyzed by repeated measures ANOVA. *P* value represents the interaction between treatment group and follow-up time. A significant interaction between the treatment group and time indicates that longitudinal change of SGA score differs between treatment and control groups.

statistically significant, and a shorter hospital stay than the placebo group (8.4 ± 17.7 versus 16.8 ± 21.7 d/yr, $P = 0.02$). Further analysis showed that the placebo group had a higher number of hospital admissions, and the duration stay was longer, in almost all entities (Table 4). Although the treatment group was marginally more likely to require admission for fluid overload than the placebo group (112 versus 89 d, $P = 0.36$), the difference was not statistically significant. There was no difference in the number or duration of hospitalization between the groups 12 mo before the study.

Mortality and Technique Failure

During the study period, 2 patients of the treatment group died. The causes of death were sudden cardiac death (1 patient) and peritonitis (1 patient). Five patients of the placebo group died. The causes of death were sudden cardiac death (2 patients), peripheral vascular disease (1 patient), mesenteric infarct (1 patient), and peritonitis (1 patient). One patient from each group was transferred to long-term hemodialysis, and 1 patient of the treatment group had kidney transplantation. At 1 yr, the treatment group had a slightly higher actuarial patient survival (93.3% versus 83.3% , log rank test, $P = 0.20$), but the difference was not statistically significant.

Discussion

Although our trial is small and has limited ability to exclude the effect of potential confounding factors, we find that oral sodium bicarbonate probably improves nutritional status and reduces hospitalization in Chinese CAPD patients with Kt/V 1.7 to 2.1 and plasma bicarbonate <24 mmol/L. In contrast, the

K/DOQI guideline recommends bicarbonate supplement in patients with plasma bicarbonate <22 mmol/L (22). Our findings suggest that treatment of mild acidosis may be beneficial.

In this study, serum bicarbonate rose in the control group during the first 4 wk. We believe the change represents a “trial effect” because all patients were informed of the nature and causes of acidosis on enrollment, which might transiently affected the diet and behavior of the enrolled patients. After 4 wk, there was gradual decline in plasma bicarbonate level in both groups, possibly due to the loss of residual renal function (23).

We chose SGA as the major outcome measure because it has proven clinical significance (2). Although SGA has only been validated as a descriptive and predictive variable, the CANUSA study showed that SGA was related to mortality and hospitalization of CAPD patients when the score was considered as a time-dependent variable (2), suggesting that SGA might be used for monitoring response to change. It should be noted that our study had limited statistical power to detect changes in other estimates of nutritional status. Estimation of statistical power by the PASS 2000 software (NCSS, Kaysville) shows that about 150 to 200 patients are required to detect the effect on FEBM and anthropometric LBM, and 370 patients are required for survival analysis to provide a statistical power of 80%. Unfortunately, because of technical difficulties in follow-up arrangement, we did not assess the actual dietary protein and caloric intake to verify an increase in protein intake. We also have no data on the dietary sodium intake, which may contribute to the difference in hospitalization for heart failure.

It should be noted that NPNA and FEBM were mathematically coupled with Kt/V and CCr, because all of them were

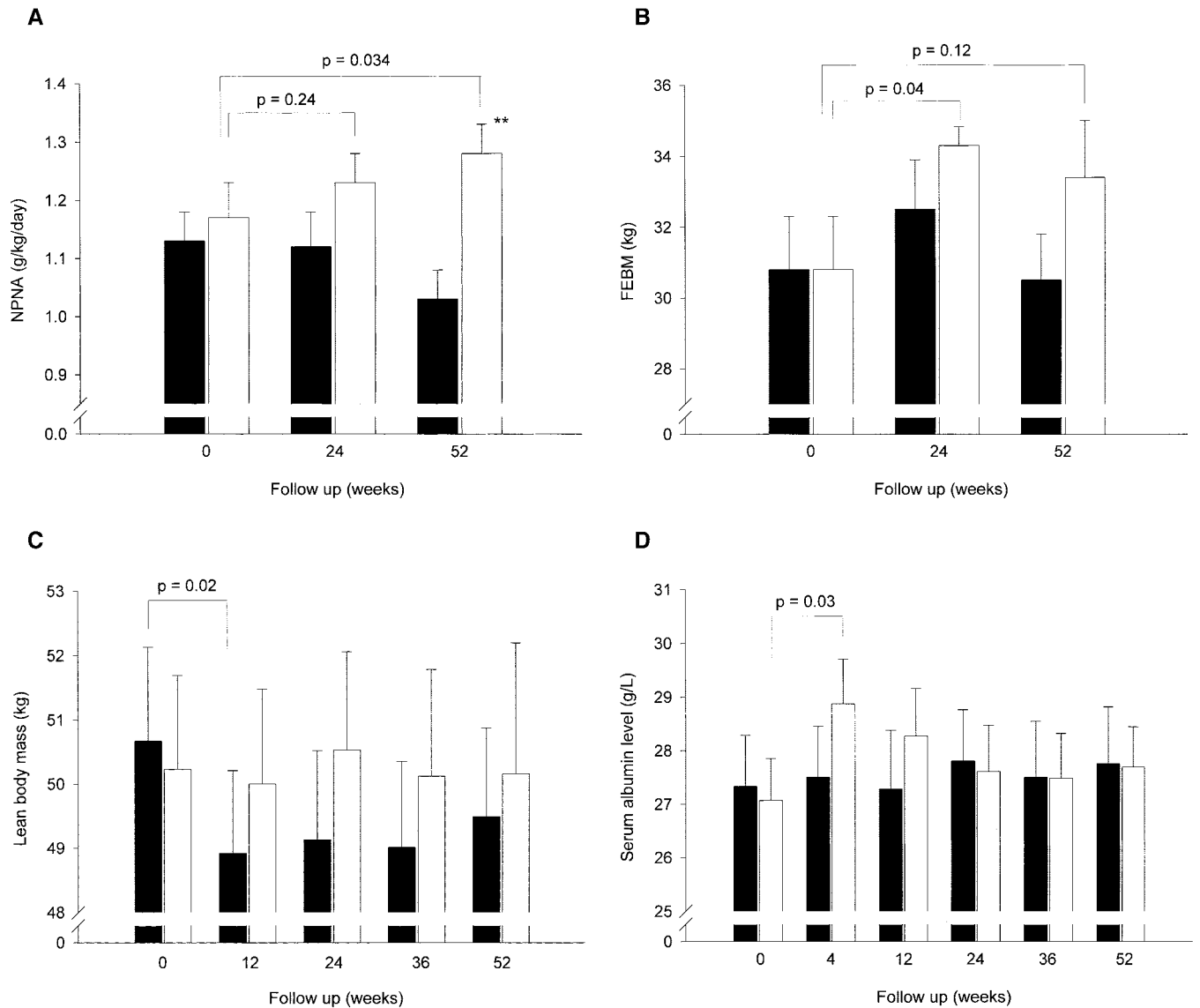


Figure 3. Other nutritional indices in the treatment group (open bars) and placebo group (closed bars). (A) Normalized protein nitrogen appearance (NPNA). (B) Fat-free edema-free body mass (FEBM). (C) Anthropometric lean body mass (LBM). (D) Serum albumin level. There was no significant difference in any index between the groups at baseline. Error bars denote SEM. $^{**}P < 0.001$ between treatment and placebo groups.

measured and calculated from the same 24-h urine and dialysate collection (24). However, the effect of mathematical coupling in longitudinal studies may not be as great as in cross-sectional studies (25). In our control group, the decline in NPNA may represent a coupling effect with decline in residual renal function rather than deterioration in nutritional status. Nevertheless, NPNA rose after sodium bicarbonate treatment, despite a similar degree of decline in Kt/V, suggesting a genuine increase in dietary protein intake.

There was substantial difference in the serum albumin level of our patient population compared with Western population (2). Serum albumin in this study was measured by bromocresol purple method, which was lower than the conventional bromocresol green method. However, even when the value was corrected with the formulae suggested by Joseph *et al.* (26), serum albumin was still

low in our subjects. Similar observation was made in our previous studies on peritoneal dialysis adequacy (13,27), but the cause of this discrepancy was not clear.

The mechanism of sodium bicarbonate is uncertain. Metabolic acidosis causes accelerated proteolysis by enhancing the activity of ATP-dependent ubiquitin-proteasome system (28) and the enzyme branch-chain ketoacid dehydrogenase (29). However, we found that bicarbonate supplement improved SGA score for anorexia and NPNA. The change in NPNA was not explained by the change in body weight and therefore likely represented a true improvement in appetite and dietary protein intake. Although the effect of oral sodium bicarbonate on appetite has not been reported, Zheng *et al.* (30) recently found that bicarbonate/lactate buffered peritoneal dialysis solutions had a positive effect on appetite.

Table 4. Summary of reasons for hospitalization

	Control Group	Treatment Group
Causes of hospitalization, no. of admission (days of hospital stay)		
heart failure or fluid overload	10 (89)	19 (122)
acute coronary syndrome	8 (112)	1 (3)
stroke	1 (5)	2 (15)
peritonitis	7 (72)	10 (36)
nonperitonitis infection	9 (39)	2 (3)
problem of dialysis access	4 (15)	0 (0)
planned admission for investigation	9 (27)	8 (24)
specific surgical problems	4 (29)	3 (12)
other specific medical problems	15 (98)	3 (16)
nonspecific	6 (17)	5 (22)
Total	73 (504)	53 (253)
Patients did not need hospitalization, no. of cases (%)	9 (30.0%)	14 (46.7%)
Hospitalization 12 mo prior to recruitment		
no. of admissions (days of hospital stay)	69 (394)	75 (364)
patients did not need hospitalization, no. of cases (%)	12 (40.0%)	12 (40.0%)

The overall magnitude of benefit observed in our study was similar to a previous report (9), which used high-lactate dialysate for the correction of acidosis. There are, however, controversial opinions about the value of treating mild acidosis in CAPD patients. For example, Kang *et al.* (31) reported a better nutritional status in patients with mild metabolic acidosis compared with those without. In the study of Stein *et al.* (9), average hospitalization was 6 d shorter in the treatment group, whereas it was 8 d in our study. It should be noted that the absolute duration of hospital stay was shorter in our patients (*e.g.*, 16.8 d/yr in the placebo group) than that reported by Stein *et al.* (21.2 d/yr) (9) and other Western series (2). Because Hong Kong is a small place and most of our patients live close to the dialysis unit (32), hospitalization for minor problems could be minimized by our extensive effort to facilitate ambulatory care.

It is important to note that the long-term effect of sodium bicarbonate supplement remains uncertain. There was a trend of more hospital admission for heart failure and fluid overload in the treatment group, which may argue against the use of sodium bicarbonate, especially in the light of the reported success of high lactate dialysate (9) and the development of bicarbonate dialysate (33). However, the difference in hospitalization for heart failure and fluid overload was not statisti-

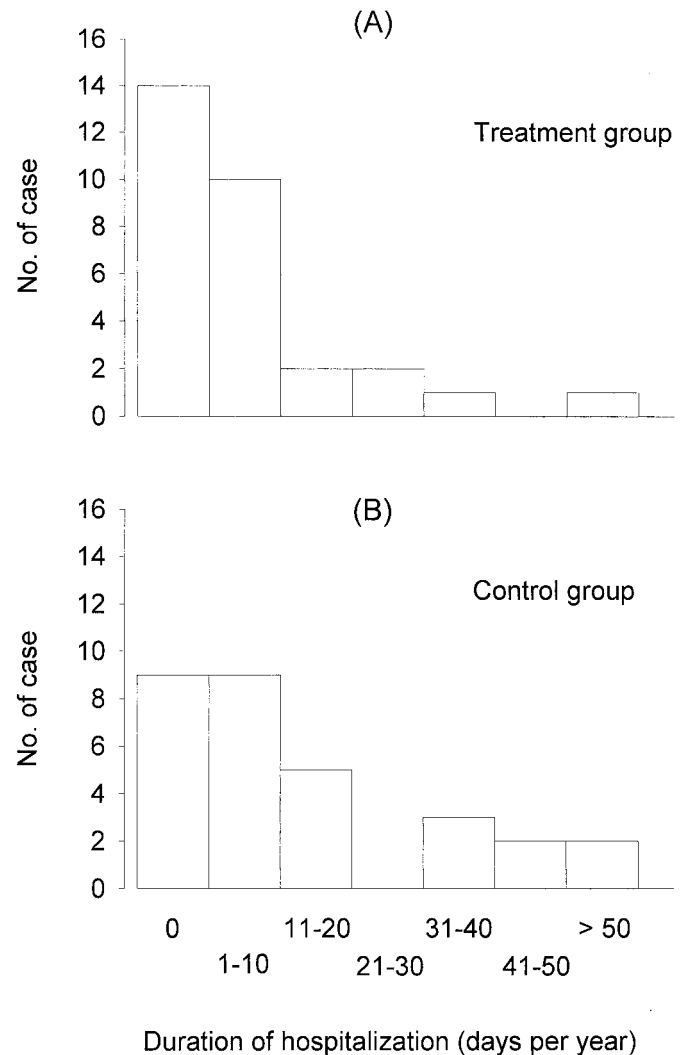


Figure 4. Frequency distribution histogram of the duration of hospitalization in 1 yr: (A) treatment group, and (B) placebo group.

cally significant, and there were somewhat more patients with pre-existing heart failure in the treatment than the control group (12 *versus* 8 patients). Clinicians should nevertheless be cautious with the potential problem of sodium load after sodium bicarbonate therapy.

Theoretically, the administration of sodium, an extracellular fluid expander, may increase the residual renal function, which may affect the morbidity and mortality (34). To control for the extracellular fluid volume changes, the ideal placebo would be sodium chloride. However, oral sodium chloride has a distinct taste that would have made blinding difficult.

Acknowledgments

This study was supported by the Hong Kong Health Services Research Committee (HSRC) research grant #931010. The authors declare no conflict of interest. We thank Janny Fung and C.C. Chow for performing nutritional assessment, and Wendy Tang from the Renal Unit, Prince of Wales Hospital, Shatin, Hong Kong, for clerical assistance. The interim results of this study have been presented as a poster in the Renal Week 2002 of American Society of Nephrology.

References

- Kaminski MV Jr, Lowrie EG, Rosenblatt SG, Haase T: Malnutrition is lethal, diagnosable and treatable in ESRD patients. *Transplant Proc* 23: 1810–1815, 1991
- CANADA-USA (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. *J Am Soc Nephrol* 7: 198–207, 1996
- Mak SK, Wong PN, Lo KY, Tong GM, Fung LH, Wong AK: Randomized prospective study of the effect of increased dialytic dose on nutritional and clinical outcome in continuous ambulatory peritoneal dialysis patients. *Am J Kidney Dis* 36: 105–114, 2000
- Blake PG, Stojimirovic B: Peritoneal dialysis adequacy and risk of death. *Curr Opin Nephrol Hypertens* 10: 749–754, 2001
- Paniagua R, Amato D, Vonesh EF, Correa-Rotter R, Ramos A, Moran J, Mujais SK: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 13: 1307–1320, 2002
- Kopple JD, Swendseid ME: Protein and amino acid metabolism in uremic patients undergoing maintenance hemodialysis. *Kidney Int* 1975: 7[Suppl 2]: 564–572
- Mitch WE: Influence of metabolic acidosis on nutrition. *Am J Kidney Dis* 29: xlv–xlviii, 1997
- Szeto CC, Lai KN: Metabolic acidosis and nutritional status of patients receiving continuous ambulatory peritoneal dialysis (CAPD). *Int J Artif Organs* 21: 192–195, 1998
- Stein A, Moorhouse J, Iles-Smith H, Baker F, Johnstone J, James G, Troughton J, Bircher G, Walls J: Role of an improvement in acid-base status and nutrition in CAPD patients. *Kidney Int* 52: 1089–1095, 1997
- Nolph KD, Prowant B, Serkes KD: Multicenter evaluation of a new peritoneal dialysis solution with a high lactate and a low magnesium concentration. *Perit Dial Bull* 3: 63–65, 1983
- Graham KA, Reich D, Channon SM, Downie S, Gilmour E, Passlick-Deetjen J, Goodship THJ: Correction of acidosis in CAPD decreases whole body protein degradation. *Kidney Int* 49: 1396–1400, 1996
- NKF-K/DOQI: Clinical practice guidelines for peritoneal dialysis adequacy: Update 2000. *Am J Kidney Dis* 37[Suppl 1]: S65–S136, 2001
- Szeto CC, Wong TY, Leung CB, Wang AY, Law MC, Lui SF, Li PK: Importance of dialysis adequacy in mortality and morbidity of Chinese CAPD patients. *Kidney Int* 58: 400–407, 2000
- Beddhu S, Zeidel ML, Saul M, Seddon P, Samore MH, Stoddard GJ, Bruns FJ: The effects of comorbid conditions on the outcomes of patients undergoing peritoneal dialysis. *Am J Med* 112: 696–701, 2002
- Enia G, Sicus C, Alati G, Zoccali C: Subjective global assessment of nutrition in dialysis patients. *Nephrol Dial Transplant* 8: 1094–1098, 1993
- Durnin JV, Rahaman MM: The assessment of amount of fat in human body from measurement of skin fold thickness. *Br J Nutr* 21: 681–689, 1967
- Forbes GB, Brunining GJ: Urinary creatinine excretion and lean body mass. *Am J Clin Nutr* 29: 1359–1366, 1976
- Bergstrom J, Heimbürger O, Lindholm B: Calculation of the protein equivalent of total nitrogen appearance from urea appearance. Which formulas should be used? *Perit Dial Int* 18: 467–473, 1998
- Department of Health, Republic of China (Taiwan). *The ROC's Handbook of Diet*, 2nd Ed., Taipei, 1994, (A) pp. 20–21
- Nolph KD, Moore HL, Twardowski ZJ, Khanna R, Prowant B, Meyer M, Ponferrada L: Cross-sectional assessment of weekly urea and creatinine clearances in patients on continuous ambulatory peritoneal dialysis. *ASAIO J* 38: M139–M142, 1992
- Van Olden RW, Krediet RT, Struijk DG, Arisz L: Measurement of residual renal function in patients treated with continuous peritoneal dialysis. *J Am Soc Nephrol* 7: 745–748, 1996
- NKF K/DOQI: *Guidelines 2000: Clinical Practice Guidelines for Nutrition in Chronic Renal Failure*. Available online at www.kidney.org/professionals/doqi/guidelines/doqi_nut.html
- Tranaeus A, Heimbürger O, Lindholm B, Bergstrom J: Six years experience of CAPD at one centre: a survey of major findings. *Perit Dial Int* 8: 31–41, 1988
- Harty J, Faragher B, Venning M, Gokal R: Urea kinetic modeling exaggerates the relationship between nutrition and dialysis in CAPD patients. (The hazards of cross-sectional analysis.) *Perit Dial Int* 15: 105–109, 1995
- Lowrie EG: Thoughts about judging dialysis treatment: mathematics and measurements, mirrors in the mind. *Semin Nephrol* 16: 242–262, 1996
- Joseph R, Tria L, Mossey RT, Bellucci AG, Mailloux LU, Vernace MA, Miller I, Wilkes BM: Comparison of methods for measuring albumin in peritoneal dialysis and hemodialysis patients. *Am J Kidney Dis* 27: 566–572, 1996
- Szeto CC, Wong TY, Chow KM, Leung CB, Law MC, Wang AY, Lui SF, Li PK: The impact of dialysis adequacy on the mortality and morbidity of anuric Chinese patients receiving continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 12: 355–360, 2001
- Mitch WE, Goldberg AL: Mechanisms of muscle wasting: The role of the ubiquitin-proteasome pathway. *N Engl J Med* 335: 1897–1905, 1997
- England BK, Greiber S, Mitch WE, Bowers BA, Herring WJ, McKean M, Ebb RG, Price SR, Danner DJ: Rat muscle branched-chain ketoacid dehydrogenase activity and mRNAs increase with extracellular acidemia. *Am J Physiol* 268: C1395–C1400, 1995
- Zheng ZH, Sederholm F, Anderstam B, Qureshi AR, Wang T, Sodersten P, Bergstrom J, Lindholm B: Acute effects of peritoneal dialysis solutions on appetite in non-uremic rats. *Kidney Int* 60: 2392–2398, 2001
- Kang DH, Lee R, Lee HY, Han DS, Cho EY, Lee CH, Yoon KI: Metabolic acidosis and composite nutritional index (CNI) in CAPD patients. *Clin Nephrol* 53: 124–131, 2000
- Lui SF, Ho YW, Chau KF, Leung CB, Choy BY: Hong Kong Renal Registry 1995–1999. *Hong Kong J Nephrol* 1: 53–60, 1999
- Passlick-Deetjen J, Kirchgessner J: Bicarbonate: the alternative buffer for peritoneal dialysis. *Perit Dial Int* 16[Suppl 1]: S109–S113, 1996
- Zoccali C: Cardiorenal risk as a new frontier of nephrology: research needs and areas for intervention. *Nephrol Dial Transplant* 17[Suppl 11]: 50–54, 2002

**Access to UpToDate on-line is available for additional clinical information
at <http://www.jasn.org/>**