

Compared effects of calcium and sodium polystyrene sulfonate on mineral and bone metabolism and volume overload in pre-dialysis patients with hyperkalemia

Yosuke Nakayama¹ · Kaoru Ueda^{1,2} · Sho-ichi Yamagishi³ · Miki Sugiyama¹ · Chika Yoshida¹ · Yuka Kurokawa¹ · Nao Nakamura¹ · Tomofumi Moriyama¹ · Goh Kodama¹ · Tomohisa Minezaki¹ · Sakuya Ito¹ · Akiko Nagata¹ · Kensei Taguchi¹ · Junko Yano¹ · Yusuke Kaida¹ · Kazutaka Shibatomi² · Kei Fukami¹

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Abstract

Background Hyperkalemia is prevalent in end-stage renal disease patients, being involved in life-threatening arrhythmias. Although polystyrene sulfonate (PS) is commonly used for the treatment of hyperkalemia, direct comparison of effects between calcium and sodium PS (CPS and SPS) on mineral and bone metabolism has not yet been studied.

Methods In a randomized and crossover design, 20 pre-dialysis patients with hyperkalemia (>5 mmol/l) received either oral CPS or SPS therapy for 4 weeks.

Results After 4-week treatments, there was no significant difference of changes in serum potassium (K) from the baseline (ΔK) between the two groups. However, SPS significantly decreased serum calcium (Ca) and magnesium (Mg) and increased intact parathyroid hormone (iPTH) values, whereas CPS reduced iPTH. $\Delta iPTH$ was inversely correlated with ΔCa and ΔMg ($r = -0.53$ and $r = -0.50$, respectively). Furthermore, sodium (Na) and atrial natriuretic peptide (ANP) levels were significantly elevated in patients with SPS, but not with CPS, whereas ΔNa and ΔANP were significantly correlated with each other in all

the patients. We also found that ΔNa and $\Delta (Na \text{ to chloride ratio})$ were positively correlated with ΔHCO_3^- . In artificial colon fluid, CPS increased Ca and decreased Na. Furthermore, SPS greatly reduced K, Mg, and NH_3 .

Conclusion Compared with SPS, CPS may be safer for the treatment of hyperkalemia in pre-dialysis patients, because it did not induce hyperparathyroidism or volume overload.

Keywords Chronic kidney disease · Potassium · Calcium · Sodium · Hyperkalemia · Secondary hyperparathyroidism

Introduction

Hyperkalemia is one of the most common complications in end-stage renal disease patients, and could cause serious electronic abnormality in the heart such as cardiac arrhythmias, thereby being involved in heart failure and sudden death in patients with advanced chronic kidney disease (CKD) [1]. Indeed, it has been reported that higher serum potassium (K) levels are associated with the increased risk of mortality in both CKD and non-CKD patients [2, 3]. Although there is a growing body of evidence that renin–angiotensin system (RAS) inhibitors have protected against the progression of renal disease and its associated organ damage in patients with advanced CKD [4, 5], the therapeutic option may be limited due to considerable side effects, such as hyperkalemia [6, 7]. Therefore, strict management of hyperkalemia is desirable for a wide variety of CKD patients to prevent adverse cardio-renal events [8, 9].

Polystyrene sulfonate (PS), a cation-exchange resin, is the most commonly used drug for the treatment of hyperkalemia [10, 11]. There are two types of PS, calcium (Ca) and sodium (Na) PS (CPS and SPS), which are cross-linked

Yosuke Nakayama and Kaoru Ueda contributed equally to this work.

✉ Kei Fukami
fukami@med.kurume-u.ac.jp

¹ Division of Nephrology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka, Japan

² Department of Rheumatology and Nephrology, Oita Prefectural Hospital, Oita, Japan

³ Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume, Fukuoka, Japan

polymers to which reactive sulfonic groups are attached and preloaded with Ca and Na, respectively [12, 13]. Although both types of PS exchange their bound cations for K in the lumen of proximal and distal colon and resultantly reduce serum K levels through the excretion of K into the stool, as far as we know, there is no head-to-head comparison prospective study of CPS vs. SPS in pre-dialysis CKD patients.

Hypocalcemia and secondary hyperparathyroidism are also prevalent in advanced CKD patients [14, 15], both of which are associated with vascular calcification and osteoporotic bone fracture [16, 17], partly contributing to the increased risk of cardiovascular disease in these patients [18, 19]. Moreover, exposure to Na-containing formulations of medicines has been shown significantly to increase the risk of cardiovascular events in humans compared with standard formulations of those same drugs [20, 21]. Therefore, in this study, we performed an open-labeled, randomized, prospective, and crossover trial to directly compare the effects of CPS and SPS on mineral and bone metabolism, including serum K, Ca, phosphate (P), magnesium (Mg), intact parathyroid hormone (iPTH) and Na levels in 20 pre-dialysis outpatients (estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m²) with hyperkalemia (serum K >5.0 mmol/l). We further examined the effects of CPS and SPS on plasma natriuretic peptide (ANP) levels in our patients and investigated whether change of ANP after PS treatments (Δ ANP) was correlated with that of Δ Na.

Materials and methods

Patients

A total of 20 pre-dialysis CKD 4–5 outpatients with hyperkalemia (K >5 mmol/l) not treated with PS were enrolled in this study. The patients were followed up at Kurume University Hospital, Oita Prefectural Hospital, and Munakata Suikokai General Hospital from October 2013 to November 2014. We excluded patients who were already given PSs, who had acute kidney injury. The etiology of renal disease was as follows: diabetic nephropathy ($n = 6$), glomerulonephritis ($n = 5$), nephrosclerosis ($n = 3$), lupus nephritis ($n = 2$), membranous nephropathy ($n = 1$), IgA nephropathy ($n = 1$), and unknown ($n = 2$). More than a half of the patients received RAS inhibitors and Ca blockers for the treatment of hypertension (55, 65%, respectively). No patients received diuretics or phosphate binders during the study period.

Study design

This study was designed as a prospective, open-labeled, randomized, and crossover study (Fig. 1). Twenty hyperkalemic patients were randomly assigned to CPS group ($n = 10$) or SPS group ($n = 10$) by an envelope method. Patients were orally administered CPS (ARGAMATE[®] 89.29% GRANULE 5.6 g; powder 5 g) or SPS (KAYEXALATE DRY SYRUP 76%[®] 6.54 g; powder 5 g) after each meal. After 4-week treatment (period 1), each PS was immediately switched to another PS without washout interval, and followed up for further 4 weeks (period 2). Blood pressure was measured in the sitting position using an upright standard sphygmomanometer.

Data collection

Before and after the switching to PS, blood was drawn from antecubital veins for determination of serum blood urea nitrogen, creatinine, K, albumin, Ca, P, Mg, Na, ammonia (NH₃), iPTH, and plasma ANP. Urine was collected for evaluation of urinary K and Na excretion levels. Blood and urine chemistries were measured at a commercially available laboratory (SRL Inc., Hachioji, Japan) as described previously [22]. We calculated corrected Ca levels by the following Ca correction formula (Payne): Ca (mg/dl) + [4 – serum albumin (g/dl)] [23]. Venous blood gas was taken to analyze the plasma bicarbonate (HCO₃⁻) levels [24].

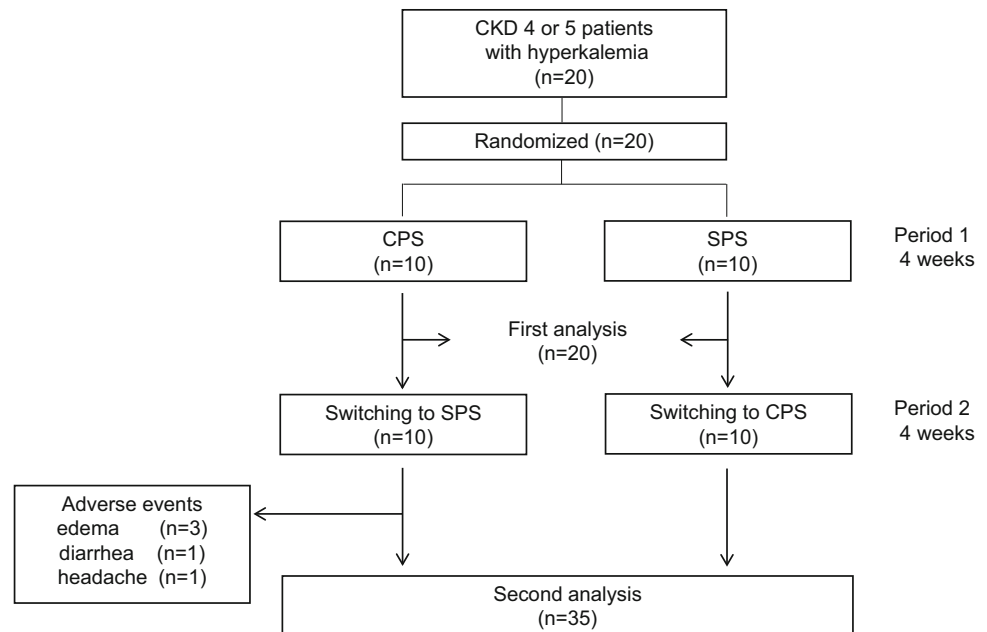
In vitro study

To investigate the cation-absorption capacity of CPS and SPS, we constructed an artificial colon fluid (ACF) based on the data of human diarrhea as described previously [25]. One gram of CPS or SPS was added into 50 ml of ACF ($n = 6$, respectively) and the solution were stirred at room temperature for 120 min. After filtration, the concentrations of K, Ca, Na, Mg, and NH₃ in the supernatant were determined.

Statistical analysis

Unless otherwise, data were expressed as mean \pm SD. Distribution of iPTH is, in general, heavily skewed; therefore, data on iPTH were presented as the median value (interquartile range). A one-way analysis of variance for repeated measures was used to assess the differences in baseline characteristics. To examine the difference of serum K, Ca, P, Na, chloride (Cl), Mg, iPTH, and ANP levels before and after the treatment with CPS or SPS in the period 1 and period 2, a paired *t* test was performed. Unpaired *t* test was performed in the comparison between

Fig. 1 Study design. CKD patients were randomized to CPS and SPS groups. After the first 4 weeks of the therapy phase (period 1, $n = 20$), CPS and SPS were immediately switched to another PS, and followed for further 4 weeks (period 2, $n = 35$). *CKD* chronic kidney disease, *PS* polystyrene sulfonate, *CPS* calcium polystyrene sulfonate, *SPS* sodium polystyrene sulfonate



CPS ($n = 20$) and SPS ($n = 15$) group. A Wilcoxon rank sum test and a Mann–Whitney U test were used for within-group differences and between-group differences of serum iPTH, respectively. All statistical analyses were performed by Graph Prism 5.0 for windows (GraphPad Software Inc. La Jolla, CA, USA) except for stepwise multiple regression analysis, which was performed to explore the independent determinants of Δ iPTH using IBM SPSS statistics ver.20 (IBM, Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

Results

Clinical characteristics of the patients

Clinical characteristics of 20 pre-dialysis outpatients with hyperkalemia are shown in Table 1. Overall, 55% of the patients were women and mean age was 69.7 ± 11.5 years. Six patients (30%) had diabetes mellitus. The mean eGFR was 15.9 ± 5.9 ml/min/1.73 m² and 45% had an eGFR < 15 ml/min/1.73 m². The mean serum K levels were 5.50 ± 0.51 mmol/l. Nutritional conditions of all subjects were almost normal. There was no significant difference of clinical data between the two groups at baseline. Medications except PS were not changed during the study period. As shown in Fig. 1, 5 patients treated with SPS dropped out due to drug-related adverse events, such as edema (3 patients), headache (1 patient), and diarrhea (1 patient).

Effects of CPS and SPS on serum and urinary levels of K

We examined serum K levels before and after the CPS and SPS treatments in period 1 ($n = 10$, respectively). As shown in Table 2, serum K and urinary K corrected for urinary creatinine (Cr) values were significantly decreased by both treatments. The change in serum K and urinary K/Cr from baseline (serum and urinary Δ K) was almost equal between the CPS and SPS group.

Effects of CPS and SPS on other mineral and bone metabolism

We next examined whether CPS or SPS treatment could affect serum Ca, P, Mg, and iPTH levels in our patients. As shown in Table 3, although serum P levels were not affected by either PS treatment, SPS, but not CPS treatment significantly decreased serum Ca and Mg levels. Furthermore, SPS treatment significantly increased serum iPTH levels, whereas CPS decreased it. In univariate linear regression analysis, Δ Ca and Δ Mg were positively associated with Δ iPTH values during the periods 1 and 2 ($n = 35$, $r = -0.53$, $p < 0.001$ and $r = -0.50$, $p < 0.01$, respectively) (Fig. 2a, b). Stepwise multiple regression analysis revealed that Δ Ca (adjusted $\beta = -0.33$, $p < 0.05$), Δ Mg (adjusted $\beta = -0.37$, $p < 0.01$), and Δ P (adjusted $\beta = 0.35$, $p < 0.05$) were independent determinants of Δ iPTH values in our patients (Table 4). Multicollinearity in these three values was not recognized.

Table 1 Baseline characteristics of the study population

Variables	Total (<i>n</i> = 20)	CPS (<i>n</i> = 10)	SPS (<i>n</i> = 10)	<i>p</i>
Age (years)	69.7 ± 11.5	69.1 ± 12.0	70.2 ± 11.7	0.98
Female No. (%)	11 (55)	6 (60)	5 (50)	0.91
Diabetes No. (%)	6 (30)	4 (40)	2 (20)	0.64
BMI(kg/m ²)	21.9 ± 3.1	21.4 ± 3.0	22.4 ± 3.3	0.78
Body weight (kg)	54.7 ± 12.2	51.9 ± 12.5	57.8 ± 11.8	0.62
Mean BP (mmHg)	91.4 ± 14.0	89.7 ± 14.2	93.2 ± 14.6	0.88
eGFR(ml/min/1.73 m ²)	15.9 ± 5.9	13.0 ± 4.7	18.7 ± 5.7	0.08
Serum Cr (mg/dl)	3.19 ± 1.35	3.79 ± 1.61	2.59 ± 0.68	0.13
Serum BUN (mg/dl)	48.8 ± 16.9	53.8 ± 21.0	45.8 ± 11.2	0.57
Serum albumin (g/dl)	3.97 ± 0.38	3.90 ± 0.44	4.04 ± 0.32	0.72
Serum Na (mmol/l)	140.8 ± 2.1	140.8 ± 2.0	140.8 ± 2.2	0.99
Serum K (mmol/l)	5.50 ± 0.51	5.39 ± 0.49	5.60 ± 0.54	0.66
Serum Cl (mmol/l)	109.6 ± 3.2	109.4 ± 3.2	109.7 ± 3.2	0.98
Serum Ca (mg/dl)	9.11 ± 0.36	9.20 ± 0.29	9.01 ± 0.41	0.51
Serum P (mg/dl)	4.08 ± 0.65	4.03 ± 0.54	4.13 ± 0.76	0.94
Serum Mg (mg/dl)	2.16 ± 0.41	2.19 ± 0.29	2.13 ± 0.53	0.95
Serum NH ₃ (μg/dl)	52.3 ± 11.3	54.2 ± 12.0	50.1 ± 10.6	0.74
Plasma ANP (pg/ml)	70.3 ± 68.0	70.8 ± 49.3	69.9 ± 85.7	0.99
Plasma HCO ₃ ⁻ (mmol/l)	21.5 ± 2.9	20.6 ± 2.2	22.4 ± 3.3	0.37
Urinary K/Cr (g/gCr)	1.6 ± 0.8	1.4 ± 0.6	1.8 ± 1.0	0.60
Urinary Na/Cr (g/gCr)	3.2 ± 1.6	3.2 ± 1.8	3.3 ± 1.5	0.99
Serum iPTH (pg/ml)	154 [106, 253 (147)]	188 [111, 313 (202)]	135 [86, 233(147)]	0.49
Medications No. (%)				
RAS inhibitors	11 (55)	8 (80)	3 (30)	
Ca blockers	13 (65)	7 (70)	6 (60)	
α, β-blockers	6 (30)	5 (50)	1 (10)	
Mg oxide	2 (10)	1 (10)	1 (10)	
Sodium bicarbonate	6 (30)	3 (30)	3 (30)	

Categorical and continuous values are expressed as % and mean ± SD or median (interquartile range), respectively. A one-way analysis of variance for repeated measures was used to assess the difference of baseline characteristics

CPS calcium polystyrene sulfonate, *SPS* sodium polystyrene sulfonate, *BMI* body mass index, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *Cr* creatinine, *BUN* blood urea nitrogen, *Na* sodium, *K* potassium, *Cl* chloride, *Ca* calcium, *P* phosphate, *Mg* magnesium, *NH₃* ammonia, *ANP* atrial natriuretic peptide, *HCO₃⁻* bicarbonate, *iPTH* intact parathyroid hormone, *RAS* renin–angiotensin system

Effects of CPS and SPS on serum and urinary Na, plasma ANP, and acid–base equilibrium

We further investigated whether the administration of CPS or SPS could affect serum and urinary Na and plasma ANP levels. As shown in Table 5, serum Na levels were significantly increased by SPS treatment, whereas decreased by CPS. Urinary Na/Cr values were modestly, but not significantly increased by SPS, whereas decreased by CPS (Table 5). Moreover, SPS, but not CPS treatment significantly increased plasma ANP levels. In univariate linear regression analysis, ΔNa was positively associated with ΔANP values during the periods 1 and 2 (Fig. 2c). Mean blood pressure and body weight were tended to increase by SPS treatment (95.3 ± 17.5 to 97.5 ± 13.4 mmHg,

$p = 0.14$, 54.6 ± 13.1 to 55.0 ± 12.8 kg, $p = 0.33$, respectively). There was a positive correlation between ΔNa and Δbody weight ($p < 0.05$, $r = 0.45$, $n = 20$) (Fig. 2d).

It has been reported that SPS induces metabolic alkalosis via the absorption of NH₃ in the colon fluid [26]. So, we next compared the effects of SPS on serum NH₃ and plasma bicarbonate (HCO₃⁻) levels with those of CPS (Table 5). SPS, but not CPS treatment significantly increased plasma HCO₃⁻ and serum Na levels, while serum NH₃ levels were not changed by either PS treatment. As shown in Fig. 3a–c, ΔNa and Δ(Na to Cl ratio) but not ΔNH₃ were positively correlated with ΔHCO₃⁻ ($r = 0.75$, $p < 0.0001$, $r = 0.84$, $p < 0.0001$, and $r = 0.06$, $p = 0.75$, respectively).

Table 2 Effects of CPS and SPS treatment on serum and urinary K levels

Serum K (mmol/l)	0 week	4 weeks	Δserum K (95% CI)	<i>p</i>
CPS (<i>n</i> = 10)	5.39 ± 0.49	4.14 ± 0.91	−1.25 (−1.90 to −0.60)	<0.01
SPS (<i>n</i> = 10)	5.60 ± 0.54	4.12 ± 0.64	−1.48 (−1.88 to −1.08)	<0.0001
<i>p</i>	0.37	0.96	0.51	
Urinary K/Cr (g/gCr)	0 week	4 weeks	Δurinary K/Cr (95% CI)	<i>p</i>
CPS (<i>n</i> = 10)	1.39 ± 0.58	0.76 ± 0.25	−0.62 (−0.99 to −0.25)	<0.01
SPS (<i>n</i> = 10)	1.75 ± 0.96	1.01 ± 0.63	−0.73 (−1.34 to −0.13)	<0.05
<i>p</i>	0.32	0.26	0.72	

K levels were compared only with before and after PS treatment in period 1 (*n* = 10, respectively). Values are expressed as mean ± SD. Statistical significance was determined using a paired *t* test (within-group differences). Statistical significance was determined using an unpaired *t* test (between-group differences) Δ change values from the baseline, *K* potassium, *Cr* creatinine, *CPS* calcium polystyrene sulfonate, *SPS* sodium polystyrene sulfonate, *period 1* after first 4 weeks of therapy phase

Table 3 Effects of CPS and SPS treatment on mineral and bone metabolism

Serum Ca (mg/dl)	0 week	4 weeks	ΔCa (95% CI)	<i>p</i>
CPS (<i>n</i> = 20)	8.96 ± 0.46	9.09 ± 0.52	0.13 (−0.10 to 0.36)	0.26
SPS (<i>n</i> = 15)	9.09 ± 0.37	8.77 ± 0.47	−0.33 (−0.54 to −0.11)	<0.01
<i>p</i>	0.37	0.07	<0.01	
Serum P (mg/dl)	0 week	4 weeks	ΔP (95% CI)	<i>p</i>
CPS (<i>n</i> = 20)	3.96 ± 1.04	3.79 ± 0.73	−0.17 (−0.44 to 0.10)	0.20
SPS (<i>n</i> = 15)	3.99 ± 0.69	4.04 ± 1.36	0.04 (−0.55 to 0.64)	0.86
<i>p</i>	0.90	0.48	0.44	
Serum Mg (mg/dl)	0 week	4 weeks	ΔMg (95% CI)	<i>p</i>
CPS (<i>n</i> = 20)	2.03 ± 0.46	2.13 ± 0.34	0.11 (−0.01 to 0.22)	0.07
SPS (<i>n</i> = 15)	2.17 ± 0.45	1.93 ± 0.48	−0.23 (−0.32 to −0.15)	<0.001
<i>p</i>	0.37	0.16	<0.001	
Serum iPTH (pg/ml)	0 week	4 weeks	ΔiPTH (interquartile range)	<i>p</i>
CPS (<i>n</i> = 20)	171 [118, 255 (137)]	122 [71, 224 (153)]	−52 [−93, 3 (96)]	<0.01
SPS (<i>n</i> = 15)	118 [75, 229 (154)]	173 [129, 244(115)]	80 [−22, 120 (142)]	<0.05
<i>p</i>	0.15	0.08	<0.001	

Values are expressed as mean ± SD. Serum iPTH levels were expressed as median (interquartile range). Statistical significance was determined using a paired *t* test (within-group differences) for serum Ca, P, and Mg. A Wilcoxon rank sum test (within-group differences) and a Mann–Whitney *U* test (between-group differences) were performed for serum iPTH

Ca calcium, *P* phosphate, *Mg* magnesium, *iPTH* intact parathyroid hormone, Δ change values from the baseline or period 1, *CI* confidence interval, *CPS* calcium polystyrene sulfonate, *SPS* sodium polystyrene sulfonate

Effects of CPS or SPS on cation-exchange capacity in ACF

As shown in Table 6, K levels in the ACF were significantly decreased by CPS or SPS; the effect of the latter was larger than that of the former. CPS and SPS had opposite effects on Ca and Na levels in the ACF; CPS increased Ca and decreased Na, and SPS vice versa. Furthermore, SPS treatment greatly reduced Mg and NH₃.

Discussion

In our human study, although K-decreasing capacity of CPS and SPS was almost equal, serum Ca and Mg levels were significantly decreased by SPS treatment compared with CPS. These findings are consistent with the previous report showing that CPS did not affect serum Ca or Mg levels in patients with chronic renal failure [10]. Furthermore, in this study, SPS treatment

Fig. 2 Pearson's correlation between **a** Δ iPTH and Δ Ca, **b** Δ iPTH and Δ Mg, **c** Δ ANP and Δ Na ($n = 35$, respectively), and **d** Δ body weight and Δ Na ($n = 20$). Δ Changes the values from the baseline or period 1, *iPTH* intact parathyroid hormone, *Ca* calcium, *Mg* magnesium, *Na* sodium, *ANP* atrial natriuretic peptide

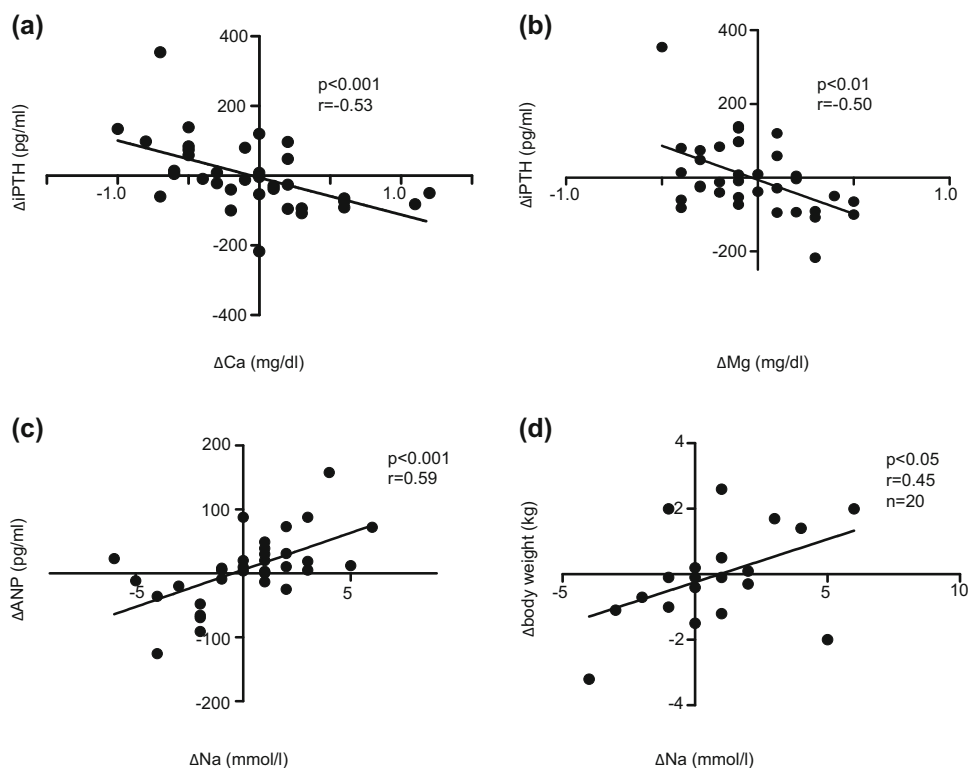


Table 4 Stepwise multiple regression analysis for Δ iPTH in pre-dialysis patients with PS treatment

	Unadjusted (β , p) $r^2 = 0.28$	Model 1 (β , p) $r^2 = 0.39$	Model 2 (β , p) $r^2 = 0.50$
Δ Ca	-0.53 ($p < 0.001$)	-0.41 ($p < 0.01$)	-0.33 ($p < 0.05$)
Δ Mg		-0.35 ($p < 0.05$)	-0.37 ($p < 0.01$)
Δ P			0.35 ($p < 0.05$)

Stepwise multiple regression analysis was performed for the independent determinants of Δ iPTH ($n = 35$). Pearson's correlation coefficient (r) and the regression line are presented. Multicollinearity was not recognized (tolerance Δ Mg = 0.86 and Δ P = 0.97)

β Standardized coefficient, Δ change values from the baseline ($n = 20$) or period 1 ($n = 15$), *iPTH* intact parathyroid hormone, *Ca* calcium, *Mg* magnesium, *P* phosphate, *PS* polystyrene sulfonate

significantly increased *iPTH* levels, whereas CPS decreased it. There was a significant and independent correlation between Δ Ca or Δ Mg and Δ iPTH values. Since SPS greatly exchanged their bound Na for K, Mg, Ca, and NH_3 in the ACF, higher cation-exchange capacity of SPS could be involved in lower serum levels of Ca and Mg, thereby worsening secondary hyperparathyroidism. In addition, although there was no significant difference of serum NH_3 between the two groups, SPS may increase intraluminal pH by absorbing NH_3 . Because higher intestinal pH has been reported to inhibit an activity of TRPM6, a major transporter of Mg in the colon [27], which could suppress the absorption of Mg, it might partly contribute to the decrease in serum Mg levels by SPS.

Parathyroid cells have calcium-sensing receptors (CaRs) on cell surface, which enable them to respond to changes in extracellular Ca concentration [28, 29]. Although Ca is the main CaR agonist, Mg is also able to activate the CaRs [30]. An increased extracellular Mg has been shown to inhibit PTH secretion by parathyroid cells [31]. Low Ca, low Mg, or high *iPTH* levels are associated with progression of diabetic kidney disease [32] and cardiovascular mortality in patients with dialysis [33]. So our present findings may raise the safety concern of SPS for the treatment of hyperkalemia in pre-dialysis patients due to its detrimental effects of Ca, Mg, and *iPTH* [18]. On the other hand, since a meta-analysis revealed that calcium supplements were associated with an increased risk of myocardial infarction [34], Ca load by CPS may also increase the risk of vascular calcification and

Table 5 Effects of CPS and SPS treatment on sodium loading and acid–base equilibrium

Serum Na (mmol/l)	0 week	4 weeks	Δ Na (95% CI)	<i>p</i>
CPS (<i>n</i> = 20)	142 ± 2.7	141 ± 2.8	−1.25 (−2.33 to 0.17)	<0.05
SPS (<i>n</i> = 15)	141 ± 2.0	143 ± 2.7	2.07 (0.99–3.14)	<0.001
<i>p</i>	0.19	<0.05	<0.001	
Urinary Na/Cr (g/gCr)	0 week	4 weeks	Δ urinary Na/Cr (95% CI)	<i>p</i>
CPS (<i>n</i> = 20)	4.1 ± 3.0	3.0 ± 1.4	−1.1 ± 2.7 (−2.4 to 0.2)	0.09
SPS (<i>n</i> = 15)	3.4 ± 1.4	5.0 ± 3.2	1.6 ± 3.5 (−0.3 to 3.5)	0.10
<i>p</i>	0.38	<0.05	<0.05	
Serum Cl (mmol/l)	0 week	4 weeks	Δ Cl (95% CI)	<i>p</i>
CPS (<i>n</i> = 20)	108 ± 3.7	109 ± 4.2	1.00 (−0.86 to 2.86)	0.27
SPS (<i>n</i> = 15)	109 ± 3.5	106 ± 4.4	−3.13 (−4.40 to −1.86)	<0.001
<i>p</i>	0.33	0.06	<0.01	
Plasma ANP (pg/ml)	0 week	4 weeks	Δ ANP (95% CI)	<i>p</i>
CPS (<i>n</i> = 20)	93 ± 81	79 ± 68	−14.0 (−36.7 to 8.8)	0.21
SPS (<i>n</i> = 15)	80 ± 76	113 ± 92	36.2 (11.1–61.2)	<0.01
<i>p</i>	0.60	0.22	<0.01	
Serum Na to Cl ratio	0 week	4 weeks	Δ Na to Cl ratio (95% CI)	<i>p</i>
CPS (<i>n</i> = 20)	1.32 ± 0.05	1.29 ± 0.04	−0.02 (−0.05 to −0.0)	<0.05
SPS (<i>n</i> = 15)	1.29 ± 0.04	1.35 ± 0.05	0.06 (0.04–0.07)	<0.0001
<i>p</i>	0.11	<0.001	<0.0001	
Plasma HCO ₃ [−] (mmol/l)	0 week	4 weeks	Δ HCO ₃ [−] (95% C.I.)	<i>p</i>
CPS (<i>n</i> = 20)	23.4 ± 4.1	20.9 ± 3.6	−2.5 (−3.7 to −1.3)	<0.001
SPS (<i>n</i> = 15)	21.2 ± 3.2	25.9 ± 4.1	4.2 (2.8–5.6)	<0.0001
<i>p</i>	0.07	<0.001	<0.0001	
Serum NH ₃ (μg/dl)	0 week	4 weeks	Δ NH ₃ (95% C.I.)	<i>p</i>
CPS (<i>n</i> = 20)	55 ± 12	54 ± 12	−0.6 (−6.0 to 4.8)	0.82
SPS (<i>n</i> = 15)	53 ± 12	54 ± 11	2.4 (−7.1 to 11.9)	0.59
<i>p</i>	0.67	0.97	0.53	

Values are expressed as mean ± SD. Statistical significance was determined using a paired *t* test (within-group differences). Statistical significance was determined using an unpaired *t* test (between-group differences). The data were in serum, urinary, and plasma samples

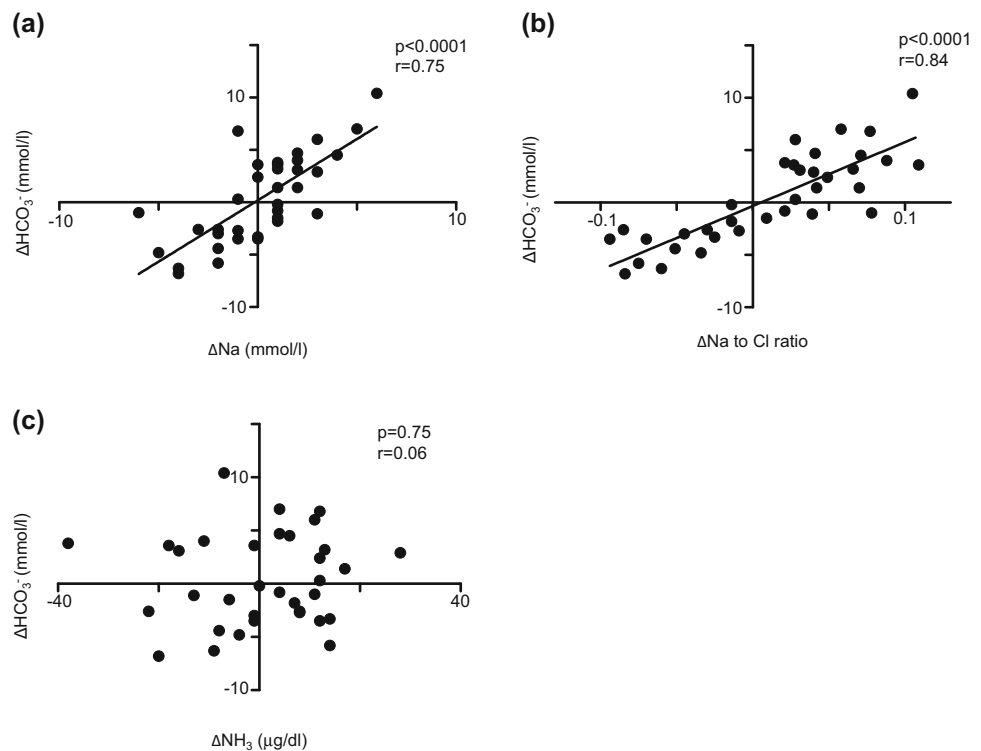
Δ change values from the baseline or period 1, *CI* confidence interval, *Na* sodium, *Cr* creatinine, *Cl* chloride, *ANP* atrial natriuretic peptide, *HCO₃[−]* bicarbonate, *NH₃* ammonia, *CPS* calcium polystyrene sulfonate, *SPS* sodium polystyrene sulfonate

cardiovascular events in CKD patients. Therefore, excess Ca intake and Ca-based phosphate binders may be avoided in CKD patients, especially those with vascular calcification.

In this study, we also found that serum Na and plasma ANP levels were significantly elevated by the treatment with SPS. Further, Δ Na was positively correlated with Δ ANP values during the study (Fig. 2c). The changes in serum Na concentration are determined not only by intestinal Na absorption, but also by water intake. Although we did not evaluate water intake in our patients, there was a positive correlation between Δ Na and Δ body weight

(*p* < 0.05, *r* = 0.45, *n* = 20) (Fig. 2d), thus suggesting that the increase of Na level by SPS might be associated with increased extracellular fluid. Recent retrospective study has shown that SPS causes inter-dialytic weight gain and increases blood pressure in dialysis patients in Dialysis Outcomes and Practice Patterns Study [35]. Exposure to sodium-containing formulations of drugs are associated with adverse cardiovascular events in patients compared to sodium-free formulation ones [20]. Therefore, intake of sodium should be strictly controlled in patients who were receiving SPS.

Fig. 3 Pearson's correlation between **a** ΔHCO_3^- and ΔNa , **b** ΔHCO_3^- and $\Delta\text{Na to Cl ratio}$, and **c** ΔHCO_3^- and ΔNH_3 ($n = 35$, respectively). Δ Changes the values from the baseline or period 1, HCO_3^- bicarbonate, NH_3 ammonia, Na sodium, Cl chloride



In the present study, although K-exchanging capacity of SPS was higher than that of CPS, serum K-reducing ability of both drugs was nearly the same. It has been reported that K concentration in lower intestine was higher than that in upper one, and the highest in distal colon [36, 37]. SPS has mainly absorbed K, Mg, Ca, and NH_3 in the fluid of upper digestive tract, where K concentration is low. On the other hand, CPS has absorbed K in the distal colon rather than upper digestive tract due to the lower cation-exchange capacity, where K concentration is highest. This might be a possible reason for the discrepant results between ACF experiments and pre-dialysis patients.

Treatment of SPS has been reported to increase HCO_3^- levels due to absorption of NH_3 in the digestive tract [26]. Consistent with the previous reports, we found that SPS, but not CPS, dramatically increased plasma HCO_3^- levels. Furthermore, although ΔNH_3 was not associated with ΔHCO_3^- values, ΔNa and $\Delta(\text{Na to Cl ratio})$ were positively correlated with ΔHCO_3^- . A close relationship between sodium as well as potassium balance and renal response to a chronic acid load was first reported in 1977 [38]. Further, Lindner et al. have shown that rising serum Na levels could cause a concurrent development of metabolic alkalosis in critically ill patients [39]. Recently

Stewart approach is proposed as a new idea of acid–base equilibrium [40, 41].

There are several limitations in this study. First, the sample size was small and the study duration was short. Second, due to the ethical concern, we could not set a washout period in this crossover study. Furthermore, as many as 5 patients were dropped out during the phase of SPS. Impaired capacity of electrolyte excretion by the kidney may affect the present findings.

Conclusion

In summary, although the present study demonstrated that K-reducing capacity of CPS and SPS was almost equal in pre-dialysis CKD patients with hyperkalemia, SPS treatment decreased Ca and Mg levels in association with increase in serum iPTH, Na, or plasma ANP values, which might lead to hyperparathyroidism and volume overload. Our present findings suggest that CPS might be better than SPS to control hyperkalemia in pre-dialysis patients. Further longitudinal studies are needed to clarify whether CPS treatment could exert more beneficial effects on bone

Table 6 Effects of CPS and SPS treatment on K, Ca, Mg, Na, and NH₃ concentrations in ACF

ACF K (mmol/l)	Before	After	ΔK (95% CI)	<i>p</i>
CPS (<i>n</i> = 6)	8.83 ± 0.08	7.60 ± 0.15	−1.23 (−1.32 to −1.15)	<0.0001
SPS (<i>n</i> = 6)	8.87 ± 0.10	6.80 ± 0.13	−2.07 (−2.24 to −1.90)	<0.0001
<i>p</i>	0.55	<0.0001	<0.0001	
ACF Ca (mg/dl)	Before	After	ΔCa (95% CI)	<i>p</i>
CPS (<i>n</i> = 6)	19.5 ± 0.19	85.5 ± 2.13	66.0 (63.8–68.2)	<0.0001
SPS (<i>n</i> = 6)	19.5 ± 0.23	5.51 ± 0.15	−14.0 (−14.3 to −13.8)	<0.0001
<i>p</i>	0.69	<0.0001	<0.0001	
ACF Mg (mg/dl)	Before	After	ΔMg (95% CI)	<i>p</i>
CPS (<i>n</i> = 6)	11.9 ± 0.47	8.92 ± 0.25	−3.0 (−3.3 to −2.6)	<0.0001
SPS (<i>n</i> = 6)	11.7 ± 0.57	5.57 ± 0.25	−6.1 (−6.5 to −5.7)	<0.0001
<i>p</i>	0.52	<0.0001	<0.0001	
ACF Na (mmol/l)	Before	After	ΔNa (95% CI)	<i>p</i>
CPS (<i>n</i> = 6)	149 ± 2.04	141 ± 3.62	−8.17 (−9.8 to −6.5)	<0.0001
SPS (<i>n</i> = 6)	150 ± 2.58	213 ± 13.8	63.0 (50.3–75.7)	<0.0001
<i>p</i>	0.55	<0.0001	<0.0001	
ACF NH ₃ (μg/dl)	Before	After	ΔNH ₃ (95% CI)	<i>p</i>
CPS (<i>n</i> = 6)	14.0 ± 0.13	12.8 ± 0.17	−1.23 (−1.40 to −1.06)	<0.0001
SPS (<i>n</i> = 6)	14.0 ± 0.16	11.7 ± 0.31	−2.34 (−2.67 to −2.01)	<0.0001
<i>p</i>	0.67	<0.0001	<0.0001	

Values are expressed as mean ± SD. Statistical significance was determined using a paired *t* test (within-group differences). Statistical significance was determined using an unpaired *t* test (between-group differences). The data were in ACF and ACF plus each polystyrene sulfonates (CPS 1 g treatment, *n* = 6 or SPS 1 g treatment, *n* = 6)

ACF artificial colon fluid, Δ change values from the before PS treatment, CI confidence interval, K potassium, Ca calcium, Mg magnesium, Na sodium, NH₃ ammonia, PS polystyrene sulfonate, CPS calcium polystyrene sulfonate, SPS sodium polystyrene sulfonate

metabolism and cardiovascular events in advanced CKD patients compared with SPS.

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Compliance with ethical standards

Conflict of interest Dr. Fukami has received honoraria such as lecture fees from Sanwa (Sanwa Kagaku Kenkyusyo). This paper has not been published previously in whole or part.

Human rights (with IRB approval number) All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethics committee at which the studies were conducted (Approval No. 13170) and with the 1964 Helsinki Declaration and its later amendments of comparable ethical standards. This trial was registered with the University Hospital Medical Information Network clinical trials database (UMIN 000021955).

Informed consent Informed consent was obtained from all individual participants included in the study.

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