Spironolactone to Prevent the Progression of Vascular Calcification among Peritoneal Dialysis Patients: A Pilot Randomised Controlled Trial (SV-CAPD trial)

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Abstract

Objective: The purpose of the study was to investigate the efficacy and safety of spironolactone to prevent vascular calcification among peritoneal dialysis patients.

Methods: This study was a randomised, double-blinded placebo-controlled trial conducted from August 2018 to December 2020 at Vajira Hospital, Thailand. We randomly assigned peritoneal dialysis patients to receive either 25 mg of spironolactone daily or a placebo for 6 months. Coronary artery calcium scores and laboratory tests were performed and compared at baseline, and 6 months thereafter.

Results: Among the 40 patients initially randomised, 34 patients completed the study (17 patients in the spironolactone group and 17 patients in the placebo group). There was no difference in baseline characteristics or laboratory results between both groups. The spironolactone group showed a significant reduction in CACs at 6 months (169.97 AU [IQR 2.34 - 1146.29] to 92.29 AU [IQR 4.83 - 851.1], p=0.05). Compared to placebo, spironolactone had a lower percentage change in CACs (0% [IQR -47.1-14.7] vs 6.06% [IQR -1.9-40.8], p=0.07. However, the change in the absolute progression of CACs was not different (0 AU [IQR -30.5-58.3] in the spironolactone group vs 6.14 AU [IQR -13.9-331.2] in the placebo group). Spironolactone also showed significantly lower serum phosphorus and osteocalcin (3.8 ± 1.3 mg/dL vs 4.8 ± 1.1 mg/dL and 69.0 ng/mL [IQR 41.9-151.5] vs 178.0 ng/mL [IQR 86.8-269.5], p=0.02 and 0.014, respectively). No hyperkalaemia or hypotension was found in either group.

Conclusion: Among peritoneal dialysis patients, spironolactone showed a potential benefit to prevent the progression of vascular calcification. Further studies with a larger population and long-term follow-up should be conducted.

Keywords: coronary artery calcium score, peritoneal dialysis, vascular calcification, spironolactone

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การศึกษาผลของยาสไปโรโนแลคโตนในการป้องกันการสะสมของผลึกแคลเซียมฟอสเฟต ในผู้ป่วยล้างไตทางช่องท้อง

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาผลของยาสไปโรโนแลคโตนในการป้องกันการสะสมของผลึกแคลเซียมฟอสเฟต และความปลอดภัยในการใช้ยาในผู้ป่วยล้างไตทางช่องท้อง

วิธีดำเนินการวิจัย: การศึกษานี้เป็นการศึกษาแบบสุ่มและมีกลุ่มควบคุมโดยใช้ยาหลอกระหว่างเดือนสิงหาคม พ.ศ. 2561 ถึงเดือนธันวาคม พ.ศ. 2563 ที่โรงพยาบาลวชิรพยาบาล ประเทศไทย สุ่มผู้ป่วยเป็น 2 กลุ่ม กลุ่มได้รับยาสไปโรโนแลคโตน 25 มิลลิกรัมต่อวัน และกลุ่มได้รับยาหลอก เป็นระยะเวลา 6 เดือน โดยทั้ง 2 กลุ่มได้รับการตรวจวัดระดับแคลเซียมในหลอดเลือดหัวใจด้วยเครื่องเอ็กซเรย์คอมพิวเตอร์ (coronary artery calcium scores) และตรวจเลือดทางห้องปฏิบัติการเกี่ยวกับระบบแคลเซียมและหลอดเลือดก่อนเริ่มการวิจัยและหลังเข้ารับการวิจัย

ผลการวิจัย: ผู้ป่วยทั้งหมด 40 คน โดยที่ผู้ป่วย 34 คน จบการศึกษา (ได้รับยาสไปโรโนแลคโตน 17 คน และได้รับยาหลอก 17 คน) โดยรวมทั้งสองกลุ่มมีลักษณะข้อมูลพื้นฐานใกล้เคียงกัน ผลการศึกษาพบว่าการได้รับยาสไปโรโนแลคโตนช่วยลดระดับแคลเซียมในหลอดเลือดหัวใจด้วยเครื่องเอ็กซเรย์คอมพิวเตอร์ได้อย่างมีนัยสำคัญทางสถิติ จาก 169.97 AU (2.34 - 1146.29) เหลือ 92.29 AU ค่า (2.34 - 1146.29) ค่านัยสำคัญทางสถิติ 0.05 นอกจากนี้กลุ่มได้รับยาสไปโรโนแลคโตนยังสามารถลดร้อยละการเปลี่ยนแปลงของระดับแคลเซียมในหลอดเลือดหัวใจด้วยเครื่องเอ็กซเรย์คอมพิวเตอร์ได้มากกว่ากลุ่มยาหลอกร้อยละ 0 (-47.1-14.7) เทียบกับร้อยละ 6.06 (-1.9-40.8) ในกลุ่มยาหลอก (ค่านัยสำคัญทางสถิติ 0.075) ส่วนผลต่างการเปลี่ยนแปลงในกลุ่มยาสไปโรโนแลคโตนได้ 0 AU เทียบกับ 6.14 AU ในกลุ่มยาหลอก (ค่านัยสำคัญทางสถิติ 0.143) ค่าเฉลี่ยการเปลี่ยนแปลงของผลเลือดทางห้องปฏิบัติการพบว่าการได้รับยาสไปโรโนแลคโตนสามารถลดระดับฟอสฟอรัสในเลือดและระดับ osteocalcin ได้อย่างมีนัยสำคัญทางสถิติ โดยที่ผลข้างเคียงไม่พบภาวะโพแทสเซียมในเลือดสูงและความดันโลหิตต่ำทั้ง 2 กลุ่ม

สรุป : การใช้ยาสไปโรโนแลคโตนมีแนวโน้มสามารถป้องกันการสะสมของผลึกแคลเซียมฟอสเฟตได้ในผู้ป่วยล้างไตทางช่องท้องได้ ผู้ศึกษาเสนอแนะให้มีการศึกษาในอนาคตเพื่อดูผลในระยะยาว เพิ่มตัวอย่าง และพิจารณาเพิ่มขนาดยาเพื่อเพิ่มประสิทธิภาพของยา

คำสำคัญ : การตรวจวัดระดับแคลเซียมในหลอดเลือดหัวใจด้วยเครื่องเอ็กซเรย์คอมพิวเตอร์ การล้างไตทางช่องท้อง ภาวะชั้นหินปูนในผนังหลอดเลือด สไปโรโนแลคโตน

วันที่รับบทความ 28 มิถุนายน 2564 **วันแก้ไขบทความ** 15 ธันวาคม 2565 **วันตอบรับบทความ** 15 ธันวาคม 2565

Introduction

Cardiovascular disease is the leading cause of death in patients with chronic kidney disease, including dialysis patients, both haemodialysis and peritoneal dialysis. Several studies have shown a strong relationship between vascular calcification, cardiovascular events and all-cause mortality. Based on clinical practice guideline updates for the diagnosis, evaluation, prevention, and treatment of CKD-MBD[1], it has been suggested that computed tomography-based imaging such as coronary artery calcium score (CACs) can be used to detect the presence or absence of vascular calcification. Many studies have confirmed that high scores for CACs are associated with major adverse cardiac events (MACE), coronary artery disease, and mortality[2-3].

The pathophysiology of vascular calcification is multifactorial and involves an increase in promotors as well as a decrease in the inhibitors of calcifications[4]. Recently, mineralocorticoid receptors were found in vascular smooth muscle cells (VSMC), leading to the hypothesis that hyperaldosteronism may be the cause of vascular calcification. Hyperaldosteronism stimulated mineralocorticoid receptors and triggered osteo-chondrogenic signalling by upregulation of PIT1 expression leading to vascular calcification[5]. Therefore, we hypothesized that spironolactone, which enables mineralocorticoid blockage, can reverse this mechanism and prevent vascular calcification.

The effect of spironolactone for the treatment of vascular calcification was found in klotho-depleted mice[6-7]. Treatment with spironolactone showed a decrease in vascular calcification without a change of calcitriol, FGF-23, serum calcium, and serum phosphate. Matsumoto and colleagues showed that 25 mg/day of spironolactone could reduce morbidity and mortality in haemodialysis patients. However, its use increases the risk of hyperkalaemia, which led to the discontinuation of the study[8]. Moreover, spironolactone showed potential benefits in peritoneal dialysis patients. Yasuhiko and colleagues showed that spironolactone could improve the left ventricular mass index and the left ventricular ejection fraction as well as preserve renal function[9]. A study in Thailand by Yongsiri and colleagues showed spironolactone may be used in the treatment of hypokalemia[10]. None of these studies revealed any serious adverse events.

Since there was no study concerning the administration of spironolactone to prevent vascular calcification in peritoneal dialysis patients, our study was conducted to evaluate this question.

Methods

The study was a prospective randomised double-blinded placebo-controlled trial carried out at Vajira Hospital, Thailand from August 2018 to December 2020. The trial was retrospectively registered at the Thai Clinical Trials Registry (TCTR20221207001) and was approved by the Vajira Institutional Review Board (IRB No. 035/62). The study was conducted in accordance with the Declaration of Helsinki and relevant regulations. The investigators informed patients or their surrogates orally concerning the study, and written informed consent was given before entry into the study.

For inclusion criteria, patients were eligible if they were aged between 18-80 years and had end-stage renal disease receiving peritoneal dialysis. Patients were excluded if they had received spironolactone within the previous 3 months, (2) persistent hyperkalaemia (defined as average serum potassium >5.5 mEq/L within 3 months), (3) persistent hypotension (defined as systolic blood pressure <90 mmHg and diastolic blood pressure <60 mmHg without other antihypertensive drugs), (4) persistent hyperphosphatemia (defined as average serum phosphate >5.5 mg/dL within 3 months), (5) hyperparathyroidism (defined as serum intact PTH >585 pg/mL), (6) dialysis vintage >10 years, (7) life expectancy <1 year due to active malignancy, infection or other diseases, (8) pregnancy or lactation female and (9) post kidney transplant or kidney transplant candidate within the last year.

Hyperkalaemia and hypotension were the most common side effects of spironolactone. Therefore, we defined withdrawal criteria as

persistent hyperkalaemia, defined as serum potassium > 5.5 mEq/L for 2 consecutive times, and hypotension, defined as SBP < 90 mmHg and DBP < 60 mmHg for 2 consecutive times without other antihypertensive drugs. Other adverse events that were or were not considered related to the study drugs were monitored in this study.

Eligible participants were randomised by using a computer-generated block of four to receive either spironolactone 25 mg daily, which was derived from a previous study[8,10], or a placebo for 6 months. Laboratory protocols including serum calcium, phosphorus, intact PTH, alkaline phosphatase, vitamin D levels, and osteocalcin were collected at baseline, 3 months and 6 months. The coronary artery calcium score (CACs) and lateral abdominal radiography were performed at baseline and 6 months thereafter. The CACs were the summation of an area of foci calcification (a calcium threshold of > 130 Hounsfield units) and calculated using the Agatston method. The lateral abdominal X-ray was interpreted using a validated grading system[11-12], of which the extent of calcification was graded on a per-segment basis using the L1-L4 vertebra segments. Per segment, a score between 0 and 3 was given for both the anterior and posterior walls of the aorta. We used scores of at least > 1 to count as vascular calcification. All imaging was read by a single experienced radiologist who was blinded to the study.

All participants were able to receive standard medications such as phosphate binders, vitamin D, erythropoietin and antihypertensive drugs, except spironolactone. However, the participants were asked to avoid over-the-counter drugs and have no adjustment of active vitamin D medication that might interfere with the outcomes.

The primary outcome was the progression of the coronary artery calcium score, consisting of absolute progression, relative progression, and significant progression of CACs. Absolute progression was defined as the difference between the initial and last scores. Relative progression was defined as the ratio between the absolute progression and the initial scores multiplied by 100. The relative progression > 15% was considered a significant progression[13-14].

The secondary outcomes were the effect of spironolactone on the biomarker of mineral-bone disorder, including serum calcium, phosphorus, intact parathyroid hormone (iPTH), alkaline phosphatase (ALP), and osteocalcin, on the effect of spironolactone to vascular calcification in lateral abdominal radiography, on the effect of spironolactone to peritoneal dialysis parameters, and adverse events of spironolactone for long-term use in peritoneal dialysis patients.

Since there was no previous study, we calculated the sample size with α of 0.05 and β of 0.2. The sample size of this study required 30 patients in each group, assumed as a drop-out rate of 10%.

The results were expressed as mean ± standard deviation for continuous normally distributed variables, median, and percentage for categorical variables. Differences in normally distributed variables were evaluated by Student's T-test, non-normal distributed by the Mann-Whitney test, and categorical variables by the Chi-square test. Statistical analysis was performed using SPSS for Windows version 22.0 with $p < 0.05$ considered statistically significant.

Results

From August 2018 to December 2020, a total of 65 patients were assessed for eligibility. A total of 25 patients were excluded, while 40 patients were randomised to receive either the intervention group or the placebo group (figure 1). Three patients in the spironolactone group were withdrawn due to death (2 patients: peritonitis infection and pneumonia with septic shock) and loss of follow-up (1 patient). Three patients in the placebo group were withdrawn due to death (1 patient: intracerebral haemorrhage) and loss of follow-up (2 patients). No follow-up data were available for these patients. In summary, 17 patients in the spironolactone group and 17 patients in the placebo group completed the study.

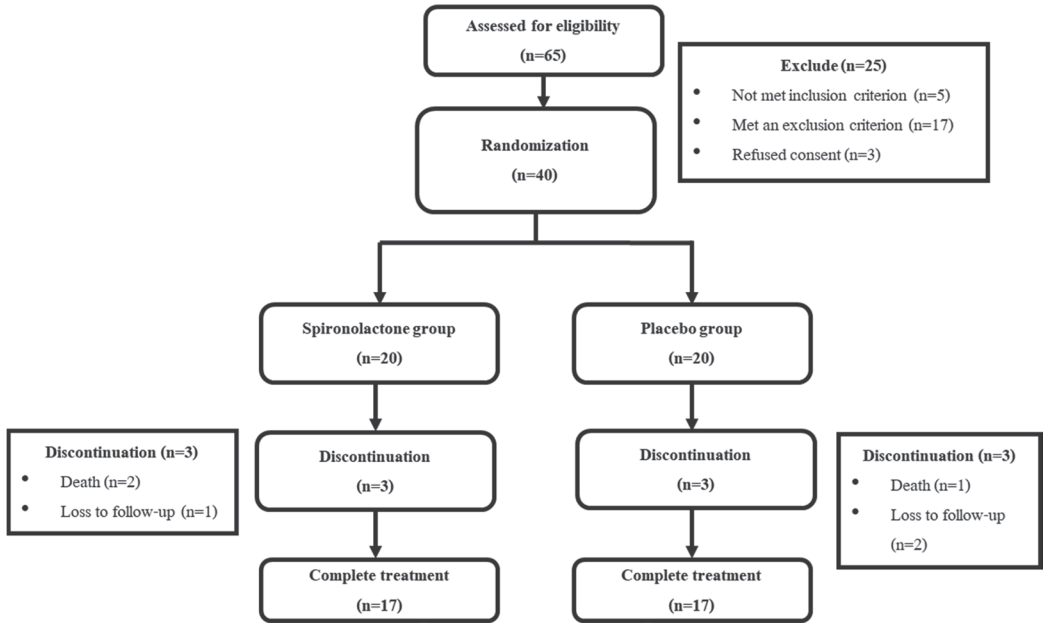

Figure 1 Participants

The baseline characteristics and laboratory data are shown in Table 1. The mean age of patients was 46 ± 15.9 years in the spironolactone group and 54.7 ± 11.9 years in the placebo group, with 64.7% being male. The leading cause of ESRD was diabetic nephropathy. There was a similarity in the medications used for both groups except for the diuretics used, which was higher in the spironolactone group (p=0.037). The baseline laboratory parameters were similar between both groups (table 1). Most of the patients were on continuous ambulatory peritoneal dialysis (CAPD) modality; the dialysis vintage was higher in the placebo group, while residual renal function was higher in the spironolactone group (table 2).

Table 1 Baseline Characteristics

Characteristics	Spironolactone	Placebo
Age, mean ± SD, y	46.0 ± 15.9	54.7 ± 11.9
Sex (Male), n (%)	11 (64.7)	11 (64.7)
Height, mean ± SD, cm	162.5±9.1	163.7 ± 9.5
Body weight, median (IQR), kg	61.0 (53.9-68.5)	59.0 (52.7-77.6)
BMI, median (IQR), kg/m^2	23.4 (20.7-26.4)	22.5 (21.5-28.1)
Underlying disease, n (%)		
Hypertension	15 (88.2)	16 (94.1)
Diabetes mellitus	11 (64.7)	12 (70.6)
Coronary artery disease	6 (35.3)	3 (17.6)

Table 1 Baseline Characteristics (continued)

Characteristics	Spironolactone	Placebo
Cause of ESRD, n (%)		
Diabetic nephropathy	9 (52.9)	10 (58.8)
Hypertensive nephropathy	4 (23.5)	4 (23.5)
SBP, mean ± SD, mmHg	136.2 ± 24.1	147.8 ± 17.0
DBP, mean ± SD, mmHg	79.7±16.2	78.1 ± 10.8
Pulse rate, mean ± SD, bpm	82.9 ± 12.8	77.1 ± 15.6
Medication, n (%)		
ACEi or ARB	6 (35.3)	11 (64.7)
CCB	15 (88.2)	15 (88.2)
Diuretics	13 (76.5)	7 (41.2)
Calcium based phosphate binder	11 (64.7)	12 (70.6)
Non-Calcium based phosphate binder	1 (5.9)	2 (11.8)
Active vitamin D	1 (5.9)	6 (35.3)
Laboratory		
Hb, mean ± SD, g/dL	10.7 ± 1.7	10.2 ± 1.1
BUN, mean ± SD, mg/dL	53.4 ± 17.3	50.5 ± 22.9
Creatinine, mean ± SD, mg/dL	9.17± 4.80	9.38±3.92
Potassium, mean ± SD, mEq/L	3.7 ± 0.6	3.9 ± 0.6
Bicarbonate, mean ± SD, mEq/L	29.7 ± 2.6	28.8 ± 3.1
Calcium, mean ± SD, mg/dL	8.3 ± 0.9	8.1 ± 1.0
Phosphate, mean ± SD, mg/dL	4.3 ± 1.0	3.9 ± 0.8
Albumin, mean ± SD, mg/dL	2.9 ± 0.5	2.7 ± 0.6
iPTH, mean ± SD, pg/dL	274.9 ± 142.5	295.9 ± 125.1
Vitamin D level, mean ± SD, ng/mL	14.8 ± 10.9	17.0 ± 11.4
Osteocalcin, mean ± SD, ng/mL	148.4 ± 123.2	225.8 ± 155.8
ALP, mean ± SD, U/L	68.7 ± 33.9	117.7 ± 60.11

Data are presented as n (%), mean ± SD, or median (interquartile range).
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ALP, alkaline phosphatase; ARB, angiotensin receptor blocker; BMI, Body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; Hb, haemoglobin; iPTH, intact parathyroid hormone; SBP, systolic blood pressure

Table 2 Baseline Peritoneal dialysis data

Peritoneal dialysis data	Spironolactone	Placebo	p-value
Mode of peritoneal dialysis, n (%)			0.60
CAPD	16 (94.1)	14 (82.4)	
APD	1 (5.9)	3 (17.6)	
Dialysis vintage, n (%), y			0.11
<1	10 (58.8)	6 (35.3)	
1-5	7 (41.2)	7 (41.2)	
>5	0 (0.0)	4 (23.5)	
Net ultrafiltration volume (mL)	600 (350-900)	800 (275-800)	0.85
Residual renal function, n (%), mL			0.035
<100	2 (11.8)	9 (52.9)	
100-500	7 (41.2)	2 (11.8)	
>500	8 (47.1)	6 (35.3)	
Peritoneal equilibrium test, n (%)			0.47
High	4 (23.5)	7 (41.2)	
High-average	9 (52.9)	6 (35.3)	
Low-average	4 (23.5)	4 (23.5)	
Dialysis adequacy (≥ 1.7) , n (%)	12 (70.6)	14 (82.4)	0.69

Data are presented as n (%) or median (interquartile range).
p-value: comparison baseline value between spironolactone group and control group; Mann-Whitney U test, Chi-square test and Fisher's exact test

The median coronary artery calcium scores (CACs) in the spironolactone group decreased statistically from 169.97 AU (IQR 2.34 – 1146.29) to 92.29 AU (IQR 4.83 – 851.1), p=0.05. In contrast, the CACs in the placebo group decreased from 424.96 AU (IQR 59.68 - 1346.34) to 450.73 AU (IQR 64.44 - 1716.17), p=0.96. The median absolute progression was lower in the spironolactone group compared to the control group, 0.00 AU (IQR -30.47 - 58.29) vs 6.14 AU (IQR -13.89 - 331.23), p=0.14. The median relative progression of CACs was also lower in the spironolactone group, 0% (IQR -47.15 - 14.69) vs 6.06% (IQR -1.87 - 40.83), p=0.07. Significant CACs progression in patients (progression of CACs more than 15%) was higher in the placebo group, but there was no statistical significance. The subgroup analysis based on the severity of CACs demonstrated no significant difference in either subgroup (table 3).

The spironolactone group had a significant decrease in mean serum iPTH (from 274.9 ± 142.5 pg/ml to 227.9 ± 123.1 pg/ml, p-value 0.045). The placebo group showed a significant increase in mean serum phosphate (from 3.9 ± 0.8 mg/dL to 4.83 ± 1.1 mg/dL, p-value 0.019). The changes in other biochemical markers of mineral-bone disorder such as mean serum calcium, mean serum vitamin D, mean serum osteocalcin and mean serum alkaline phosphatase revealed no significant differences within the group. However, there were significant differences in mean serum phosphate and mean serum osteocalcin between the spironolactone group and the placebo group (p-values of 0.02 and 0.014, consecutively) (table 4).

Table 3 Progression of coronary artery calcium scores

	Spironolactone	Placebo	p-value[b]
Coronary artery calcium scores (CACs)			
Baseline, median (IQR), AU	169.97 (2.34 - 1146.29)	424.96 (59.68 - 1346.34)	0.51
Final, median (IQR), AU	92.29 (4.83 - 851.1)	450.73 (64.44 - 1716.17)	0.22
p-value[a]	0.05	0.96	
Absolute progression, median (IQR), AU	0.00 (-30.47 - 58.29)	6.14 (-13.89 - 331.23)	0.14
Relative progression, median (IQR), %	0 (-47.15 - 14.69)	6.06 (-1.87 - 40.83)	0.07
Progression > 15 %, n (%)	4 (23.5)	7 (41.2)	0.27
Subgroup analysis			
CACS 0-100 (n=12)			
Relative progression, median (IQR), %	0 (-58.87 - 23.29)	0 (0 - 100)	0.32
Progression > 15 %, n (%)	2 (25.0)	1 (25.0)	1.00
CACS 101-399 (n=6)			
Relative progression, median (IQR), %	-23.92 (-45.7 - -2.14)	-2.28 (-11.83 - 28.49)	0.36
Progression > 15 %, n (%)	0 (0.0)	1 (25.0)	1.00
CACS ≥400 (n=16)			
Relative progression, median (IQR), %	8.74 (-48.61 - 17.15)	27.41 (1.16 - 40.83)	0.13
Progression > 15 %, n (%)	2 (28.6)	5 (55.6)	0.36

Data are presented as median (interquartile range) and n (%).
p-value[a] : comparison within group by Wilcoxon signed-rank test, p-value[b] : comparison between spironolactone group and control group by Mann-Whitney U test
CACs, coronary artery calcium score

As shown in Table 4, the spironolactone group was significantly decreased in terms of vascular calcification compared to the placebo group (p-value 0.031).

There was no difference in residual renal function or net ultrafiltration volume between both groups. The number of patients who had a reduction in residual renal function showed no significant difference between groups, with no patients in the spironolactone group and one patient in the placebo group (p-value 0.27). There was no significant difference in the mean net ultrafiltration volume between groups (800 ml in the spironolactone group and 800 ml in the placebo group, p-value 0.48).

No hyperkalaemia or hypotension was found in this study. The spironolactone group had 2 patients who died from infected peritonitis and pneumonia with septic shock. Meanwhile, the placebo group had a patient who died from intracerebral haemorrhage. The other adverse events are reported in Table 5.

Table 4 Change in biochemical parameters

	Spironolactone		Placebo		p-value[b]
	Baseline	Final	Baseline	Final	
Hb, g/dL	10.7 ± 1.7	10.1 ± 2.1	10.2 ± 1.1	10.5 ± 1.2	0.40
BUN, mg/dL	53.4 ± 17.3	47.8 ± 18.1	50.5 ± 22.9	52.1 ± 22.8	0.55
Creatinine, mg/dL	9.2 ± 4.8	9.3 ± 5.2	9.4 ± 3.9	9.9 ± 4.0	0.72
Potassium, mEq/L	3.7 ± 0.6	3.7 ± 0.4	3.9 ± 0.6	3.7 ± 0.6	0.89
Bicarbonate, mEq/L	29.7 ± 2.6	30.0 ± 2.3	28.8 ± 3.1	28.3 ± 2.6	0.05
Calcium, mg/dL	8.3 ± 0.9	7.9 ± 0.7	8.1 ± 1.0	7.9 ± 0.9	0.95
Phosphate, mg/dL	4.3 ± 1.0	3.8 ± 1.3	3.9 ± 0.8	4.8 ± 1.1[a]	0.02
Albumin, mg/dL	2.9 ± 0.5	2.8 ± 0.6	2.7 ± 0.6	2.7 ± 0.4	0.79
iPTH, pg/dL	274.9 ± 142.5	227.9 ± 123.0[a]	295.9 ± 125.1	299.0 ± 228.4	0.27
Vitamin D level, ng/mL	12.1 (6.9-18.2)	17.7 (11.0-29.9)	11.8 (8.9-25.5)	20.6 (13.2-25.6)	0.62
Osteocalcin, ng/mL	119.0 (47.1-195.5)	69.0 (41.9-151.5)	216.0 (94.5-282.0)	178.0 (86.8-269.5)	0.014
ALP, U/L	68.7 ± 33.9	86.1 ± 38.5	117.7 ± 60.1	106.0 ± 59.8	0.26
Lateral abdominal radiography					0.031
No calcification	11 (64.7)	14 (82.4)	7 (41.2)	8 (47.1)	
Calcification	6 (35.3)	3 (17.6)	10 (58.8)	9 (52.9)	

Data are presented as n (%), mean ± SD, or median (interquartile range).
p-value[a] comparison within group by Paired sample t-test, Wilcoxon signed-rank test, and McNemar's test.
p-value[b] comparison final value between spironolactone group and control group; Mann-Whitney U test, and Chi-square test.
Abbreviations: Hb, haemoglobin; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone

Table 5 Adverse events

	Spironolactone	Placebo
Minor adverse event	4 (20%)	3(15%)
Nausea and vomiting	0	2(10%)
Gynecomastia	2(10%)	0
Common cold	2(10%)	1(5%)
Hyperkalaemia	0(0%)	0(0%)
Hypotension	0(0%)	0(0%)
Serious adverse event		
Infected peritonitis	3(15%)	1(5%)
Volume overload	2(10%)	2(10%)
Pneumonia	1(5%)	0
Sepsis	0	1(5%)
Seizure	1(5%)	0
Intracerebral haemorrhage	0	1(5%)
Death	2(10%)	1(5%)

Data were presented as n (%)

Discussion

SV-CAPD was the first pilot randomised double-blind placebo-controlled trial to demonstrate the efficacy of spironolactone to prevent the progression of vascular calcification in peritoneal dialysis patients. Despite the impressive results of spironolactone in klotho-depleted mice, our study showed 25 mg of spironolactone daily had no statistical significance in decreasing the progression of CACs compared to placebo. The absolute progression and relative progression of CACs were lower in the spironolactone group, but there was no statistical significance.

The administration of spironolactone to prevent vascular calcification using CACs was first demonstrated by Gueiros and colleagues in Brazil[15]. The result was comparable to our study in that spironolactone tended to prevent the progression of CACs. However, that study had some limitations such as small sample size and limitations of the blind. Our study utilised a larger sample size with 40 patients enrolled, and 34 patients who completed the study. Interestingly, our study showed a significant decrease in CACs in the spironolactone group (169.97 AU [IQR 2.34 - 1146.29] to 92.29 AU [4.83 - 851.1], p=0.05) compared to the placebo group, which was no improvement in CACs (424.96 AU [IQR 59.68 - 1346.34] to 450.73 AU {[IQR 4.44 - 1716.17], p=0.96). When comparing the relative progression of CACs, however, which was the more accurate result for interpretations of the progression of CACs, the efficacy of spironolactone was better but showed no statistical significance (0 AU [IQR -47.15 - 14.69] vs 6.06 AU [IQR -1.87 - 40.83], p=0.07. The result was the same with the absolute progression of CACs (table 3).

The mechanism of spironolactone to prevent vascular calcification was the inhibition of the mineralocorticoid receptors on vascular smooth muscle cells (VSMC). In our study, spironolactone had a significant improvement in serum osteocalcin levels. Since serum osteocalcin was a marker of bone formation, spironolactone may prevent the progression of vascular calcification as a result of this mechanism[16-17]. However, one of the potential causes of improvement in CACs in the spironolactone group may be from the enhanced control of serum phosphate. In our study, the mean serum phosphate at the end of the study was decreased in the spironolactone group compared to the placebo group. In contrast to previous studies[18], spironolactone did not affect serum phosphate. Thus, the spironolactone group might have better dietary phosphate control than the placebo group, or there was an unknown mechanism of spironolactone to decrease serum phosphate.

In this pilot study, we did not demonstrate the other potential benefits of spironolactone in peritoneal dialysis, such as cardiovascular outcomes, improvement of hypokalaemia, or prevention of the progression of peritoneal fibrosis. However, our study showed the safety of spironolactone for long-term use. In contrast to haemodialysis patients[8], the adverse effects of spironolactone, such as hyperkalaemia and hypotension, were not found in our study. Other adverse events were not significantly different in either group (2 deaths in the spironolactone group and 1 death in the placebo group). Therefore, our study assured that spironolactone 25 mg per day should be noted to be safe for long-term use in peritoneal dialysis patients.

Our study had several strengths. Firstly, our study was the first randomised double-blinded placebo-controlled trial to demonstrate the effect of spironolactone in preventing the progression of vascular calcification. Secondly, spironolactone is cost-effective, so it can be widely used in both well-resourced and limited-resourced facilities to prevent vascular calcification in peritoneal dialysis patients. Moreover, our study also showed the safety of spironolactone for long-term use in peritoneal dialysis patients.

Our study also had several limitations. Firstly, it used a low number of patients. We calculated a sample size of 60 patients, but only 40 patients undertook the study. Secondly, short follow-up periods were used. Previous trials had suggested a

follow-up period for the CACs of 12 to 24 months. However, some studies[20] showed the benefit of spironolactone to decrease left ventricular hypertrophy during a 6-month follow-up period. As a pilot study, we showed the effect of spironolactone to potentially prevent vascular calcification with 6-month follow-up periods. A longer follow-up period could show significant effects. Thirdly, the CACs in the spironolactone group were lower than in other previous cohort studies[19]. In our study, the CACs in the spironolactone group were 169.97 AU (IQR 2.34 - 1146.29), while the previous cohort study was 492 AU (IQR 92-1139). Finally, the dosage of spironolactone was fixed at 25 mg/day. Therefore, increasing the dose might improve the outcomes.

Conclusion

Spironolactone tends to prevent the progression of the coronary artery calcium score. A large population and a longer follow-up period are needed to confirm this hypothesis. Since there was no hyperkalaemia or hypotension in our study, the dose of spironolactone could be increased to attenuate the effects.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

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