The Effects of Sulodexide on the Prevention of Peritoneal Membrane Changes in Peritoneal Dialysis Patients

ผลของยาซูโลเด็กไซด์ต่อการป้องกันการเปลี่ยนแปลงเยื่อบุช่องท้องในผู้ป่วยที่ได้รับการล้างไตทางช่องท้องแบบต่อเนื่อง

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Abstracts

The objective of this placebo-controlled clinical study was to investigate the effects of sulodexide on the prevention of peritoneal membrane changes in CAPD patients by evaluating peritoneal membrane transports. A total of 66 patients, divided into 33 patients for each group, were included in this randomized control trial study. Patients were randomly assigned to receive either oral sulodexide 100 mg/day or a placebo. A 4-hour peritoneal equilibrium test was performed to evaluate peritoneal transport function. 61 patients completed the 3-month study. After the treatment period, there was a significantly lower D/P creatinine in the sulodexide group than in the placebo group (p-value = 0.04). However, no significant difference in D/D_0 glucose was observed between the two groups. For ultrafiltration volume, there was a significantly higher volume in the sulodexide group when compared to the placebo group (p-value = 0.01). Besides, adverse event of sulodexide was not different from the placebo group. In conclusion, the administration of oral sulodexide has a potentially beneficial effect in the prevention of peritoneal membrane damage in PD patients.

Keywords : Sulodexide, peritoneal dialysis, peritoneal membrane

Introduction

End-stage renal disease (ESRD) is a global public health problem. Peritoneal dialysis (PD) is a replacement therapy used by approximately 11% of patients with ESRD worldwide.[1] The Thai government has implemented a “PD first” policy to Thai ESRD patients under the Universal Health-Care Coverage (UC) scheme, encouraging the use of PD as an initial treatment of patients with ESRD.[2] In Thailand, the annual growth rate of ESRD patients undergoing PD in 2015 was 369 per million population and the number of PD patients rose from 2009 which was only 81 per million population.[3] Although PD is more cost-effective compared to hemodialysis (HD),[4] there are

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limitations in using PD as a long-term treatment. Structural and functional changes of the peritoneal membrane can occur during PD. Continuous exposure of the peritoneal membrane to bioincompatible dialysis solutions, peritonitis, uremia, and chronic inflammation during PD induces structural and functional changes and limit the long-term viability of the technique.[5] Phenotypic changes in peritoneal mesothelial cells may induce peritoneal sclerosis characterized by the exfoliation of mesothelial cells from the basement membrane, progressive thickening of the submesothelial compact zone, and vascular alterations including vasculopathy and neoangiogenesis.[5-8] Structural peritoneal membrane changes are believed to induce functional impairment. Increased effective peritoneal surface area and impaired free water transport are the main causes of peritoneal functional changes.[9, 10]

The prevalence of peritoneal membrane dysfunction as a cause of PD drop-out has been reported to be between 1.7% and 13.7%,[11] therefore it is important to prevent peritoneal membrane dysfunction in PD patients in order to prolong the time before switching to HD. The use of glycosaminoglycans is one of the preventive options. Heparin belongs to the glycosaminoglycans family. There are some data that heparin has shown beneficial effects in the reduction of the peritoneal membrane change apart from its anticoagulant effect.[12, 13] However, heparin use has some limitations due to its side effects and inconvenient mode of administration.[14, 15] Thus, sulodexide is considered to be an alternative option in this family. Sulodexide, which is a mixture of glycosaminoglycan consisting of fast moving heparin 80% and dermatan sulfate 20%,[16] can be administered orally and appears to have fewer side effects than heparin.[15] Sulodexide has been used as an antithrombotic drug and to reduce proteinuria in diabetic nephropathy. Besides, it has been reported to decrease peritoneal membrane dysfunction. Previous studies in animal models reported that sulodexide administered intraperitoneally, subcutaneously and orally could decrease peritoneal membrane alteration.[17-19] Several uncontrolled clinical studies found that sulodexide administered orally and intraperitoneally could also decrease peritoneal membrane dysfunction,[20, 21] but so far no good design randomized placebo-controlled clinical study has been conducted to investigate the efficacy and safety of orally administered sulodexide in preventing peritoneal membrane changes. We therefore aimed to study, in this randomized placebo-controlled study, whether sulodexide might have the advantage for peritoneal membrane preservation in PD patients.

Objectives

To determine the effects of sulodexide on the prevention of peritoneal membrane change in PD patients by evaluating peritoneal membrane transports and safety.

Methods

Patients. Study population was CAPD (continuous ambulatory peritoneal dialysis) patients. Study sample was CAPD patients who were treated at Phramongkutklao Hospital, and Banphaeo Hospital (Prommitr branch), Bangkok, Thailand during November 2015 - January 2018. The sample size calculating formula for mean difference as followed;

$$n/group = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{d^2}$$

Define, n/group = sample size in each group, α = 0.05, β = 0.20, $Z_{\alpha/2} = Z_{0.05/2}$ = 1.96 (2-tailed), $Z_{\beta} = Z_{0.20}$ = 0.84, d = the difference in dialysate cancer antigen 125 level between treatment and control group was 12 U/ml, data based on previous study.[22] σ^2 = variability of endpoint derived from the following calculation.

Pooled variance (Sp^2), using data from previous studies.[22]

$$Sp^2 = \frac{S_1^2 + S_2^2}{2}$$

$$Sp^2 = \frac{(10.6)^2 + (19.3)^2}{2} = 242.42$$

Therefore; $$n/group = 2(1.96 + 0.84)^2 \frac{242.42}{12^2}$$

$$= 26.40 \sim 27 \text{ patients/group}$$

Calculate for the drop-out rate 20% as followed

$$n/group^* = n/group + (n/group \times \frac{20}{100})$$

$$n/group^* = 27 + 5.4 = 32.4 \sim 33 \text{ patients/group}$$

The number of patients needed for this study was at least 66, divided into 2 groups. We enrolled a total of 66 patients over the age of 20 who were treated with CAPD with conventional PD solution for at least 6 months. Exclusion criteria were as follows: previous therapy with sulodexide or heparin in the previous 1 month; having infectious peritonitis or had >1 peritonitis episode or had peritonitis episode in the 3 months before the study; high peritoneal solute transport (dialysate/plasma (D/P) creatinine >0.81 or D/D_0 glucose <0.27); having coagulopathy or ongoing anticoagulant drug therapy; refusal or unable to provide informed consent.

This study was approved by the institutional review boards and ethics review committees of the Royal Thai Army Medical Department, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand (No. Q022h/56). Informed written consent was obtained from all participants.

Data collection and analysis. Patients were randomly assigned to receive either sulodexide or placebo by using a permuted block of 4. Patients did not know which treatment they received. Patients in the sulodexide group were assigned to take sulodexide 50 mg 2 times daily, orally before meal for 90 days, while patients in the placebo group were assigned to take placebo with the same administration and duration. Patients were scheduled to follow-up every 30 days. Medication adherence was assessed at each visit using pill counts and interview.

Peritoneal membrane function was evaluated by 4-hour peritoneal equilibrium test (PET), using 2 liters of 2.5% glucose PD solution at baseline and at the end of treatment period. Peritoneal fluid was sampled from the drained effluent before the test, from the test bag at 0, 120 and 240 minutes after drainage. The serum was sampled at 120 minutes after drainage. Peritoneal membrane transport was calculated by D/P creatinine, D/D_0 glucose. Net ultrafiltration was calculated as the difference between the drained and the instilled volume.

Adverse events were collected by using a self-applied record form and interview. Physical examination and laboratory evaluations were performed at baseline and end of treatment.

Compliance was assessed by the investigator at each visit using pill counts and interview. This information was recorded in monitoring record form. Patients' compliance should be at least 80% during the study period. The percentage of adherence was calculated as follows.

$$\frac{\text{Number of Pills Absent in Time} \times 100}{\text{Number of Pills Prescribed for Time}} = \%\ \text{Compliance}$$

Statistical analysis. The statistical analysis was performed using the SPSS version 17.0 (SPSS. Co., Ltd., Bangkok Thailand) which defined significant levels at $\alpha = 0.05$. The difference between peritoneal membrane transport was assessed using the Mann Whitney U-test for between group and the Wilcoxon signed - rank test for within group. The difference in adverse event rates was assessed using the chi-square test.

Results

A total of 66 patients, divided into 33 patients for each group, were included in this randomized control trial study. There were 5 patients who dropped out of the study (3 patients because of peritonitis and 2 patients because of adverse events tolerance). Overall, 61 patients completed the 3-month treatment period (30 patients in the sulodexide group, 31 patients in the placebo group). Baseline characteristic data from patients in each group are shown in Table 1. The two groups were similar for all characteristics including duration of PD, comorbid disease, previous peritonitis episode, ACEI/ARB (angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker) treatment which is believed to have a beneficial effect in preserving peritoneal membrane, peritoneal dialysis adequacy (total weekly Kt/v; renal urea clearance) and peritoneal dialysis regimen.

Table 1 Baseline clinical characteristic of study patients

Characteristic Data	Sulodexide (n=33)	Placebo (n=33)	p-value
Female (n, %)	19 (57.6)	17 (51.5)	0.75
Age ± SD (years)	56.91 ± 8.24	53.94 ± 7.62	0.55
Body weight ± SD (kg)	55.91 ± 11.82	59.76 ± 10.65	0.74
Height ± SD (cm)	155.0 ± 7.7	157.7 ± 9.2	0.82
	[140.0 – 173.0]	[144.0 – 178.0]	
Duration of PD (months)	9.8	11.1	0.47
Comorbid diseases (n, %)			0.51
Hypertension	24 (72.7)	28 (84.8)	
Diabetes mellitus	16 (48.5)	14 (42.4)	
Dyslipidemia	17 (51.5)	16 (48.5)	
Coronary artery disease	4 (12.1)	6 (18.2)	
Others	7 (21.2)	10 (30.3)	
Using ACEI/ARB	9	12	0.43
Systolic blood pressure ± SD (mmHg)	134.05 ± 19.27	138.26 ± 19.84	0.69
Diastolic blood pressure ± SD (mmHg)	83.18 ± 15.63	88.40 ± 15.19	0.14
AST (u/L)	28.9 (10.7)	23.5 (7.4)	0.44
ALT (u/L)	25.2 (15.4)	24.3 (15.7)	0.86
Serum albumin ± SD (gm/dL)	3.5 ± 0.4	3.4 ± 0.6	0.92
Total weekly Kt/v ± SD (L/L)	1.9 ± 0.5	1.8 ± 0.5	0.38
	[1.3 – 2.5]	[1.3 – 2.4]	
Patients with previous peritonitis (n, %)	11 (33.3)	15 (45.4)	0.31
Number of peritoneal solution ± SD (bags/day)	3.97 ± 0.3	3.94 ± 0.2	0.66
Peritoneal dialysis dose ± SD (L./day)	7.94 ± 0.6	7.88 ± 0.5	0.66
Concentration of peritoneal solution			
1.5% dextrose (n, %)	30 (90.9)	29 (87.9)	0.73
2.5% dextrose (n, %)	3 (9.1)	4 (12.1)	

Remarks: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; AST = aspartate aminotransaminase; ALT = alanine aminotransaminase; Kt/v = fractional urea clearance (K = dialyzer clearance, t = time, v = distribution volume of urea)

Peritoneal transport functions. Peritoneal transport functions were assessed by using a 4-hour peritoneal equilibrium test (Table 2). Results from per-protocol analysis were reported. After the treatment period, there was a significantly lower D/P creatinine in the sulodexide group than in the placebo group (p-value = 0.04). However, no significant difference in D/D_0 glucose was observed between the two groups. For 4-hour ultrafiltration volume, there was a significantly higher volume in the sulodexide group when compared to the placebo group (p-value = 0.01). The change at end point for each parameter was also calculated, the significant differences were also found only in D/P creatinine and 4-hour ultrafiltration volume.

Table 2 Peritoneal transport and ultrafiltration characteristics in sulodexide and placebo group

Parameters		Sulodexide (n=30)	Placebo (n=31)	p-value
D/P creatinine	Baseline	0.62 ± 0.09	0.63 ± 0.06	0.62
	After treatment	0.65 ± 0.08	0.70 ± 0.09	0.04*
	Change at end point	0.03 ± 0.04	0.08 ± 0.03	0.02*
D/D_0 glucose	Baseline	0.37 ± 0.12	0.38 ± 0.12	0.81
	After treatment	0.41 ± 0.13	0.39 ± 0.12	0.35
	Change at end point	0.04 ± 0.05	0.02 ± 0.07	0.32
4-hour Ultrafiltration (mL)	Baseline	777.4 ± 268.6	799.3 ± 243.6	0.08
	After treatment	657.7 ± 341.0	632 ± 291.9	0.01*
	Change at end point	- 109.2 ± 56.4	- 170.8 ± 63.1	0.01*

*p-value < 0.05

Remarks: D/P = dialysate/plasma; D/D_0 = dialysate glucose concentration at indicated time/dialysate glucose concentration

Adverse events. Patients in sulodexide and placebo group had reported adverse events during the treatment period (Table 3). There was no statistically significant difference between the two groups (p-value = 0.64). The most common adverse event was gastrointestinal discomfort which included flatulence, dyspepsia, nausea, and heartburn. Other adverse events were diarrhea, hair loss, headache, and dizziness. There were 5 patients who dropped out from the study (3 patients dropped out from peritonitis and 2 patients dropped out because they could not tolerance to gastrointestinal discomfort and diarrhea). No abnormal Hb (hemoglobin), Hct (hematocrit), Plt (platelet count), aPTT (activated partial thromboplastin time), and PT (prothrombin time) were reported in both groups.

Table 3 Adverse events in sulodexide and placebo group

Adverse events	Sulodexide (n=33)	Placebo (n=33)
Gastrointestinal discomfort	3	5
Diarrhea	1	1
Hair loss	0	1
Headache	1	0
Dizziness	2	1
Peritonitis	2	1

Compliance. During the treatment period, there were 2 patients who had compliance of less than 80%. They stopped taking the pill due to the inability to tolerate the adverse events which occurred during the study. Consequently, they were excluded from the study.

Discussion

This study was conducted to investigate the effects of oral sulodexide on the prevention of peritoneal membrane change in PD patients. The effect on peritoneal membrane transport, which reflects the functional changes of the peritoneal membrane, was explored. Results from 4-hour peritoneal equilibrium test showed that there was a significantly lower D/P creatinine in the sulodexide group than in the placebo group after the treatment period. There are several previous studies that reported contrasting results with our study, in which D/P creatinine had increased after the administration of sulodexide in CAPD patients.[20, 21, 23] However, these previous studies had a difference in research methodology with our study. In their studies, they were uncontrolled clinical trials with a small number of patients and sulodexide was administered by intraperitoneal route except in Fracasso et al.[21] study, which had oral route of administration. In contrast, no significant difference in D/D_0 glucose between two groups after the treatment period was found in our study. Fracasso et al.[21] reported the same finding that D/D_0 glucose value did not change. Indeed, D/P creatinine and D/D_0 glucose reflect peritoneal membrane transport status. In long-term PD patients whose peritoneal membrane had deteriorated, there is an increase in small solute transport rate or higher transport status defined by an increase in D/P creatinine and a decrease in D/D_0 glucose.[24] An animal model of PD conducted by Pletinck et al.[19] indicated that D/P creatinine was increased and D/D_0 glucose was decreased in the control group when compared to the sulodexide group. Therefore, our findings supported that sulodexide contributes to the preservation of peritoneal membrane transport alteration by decreasing D/P creatinine. The reason why D/D_0 glucose had no difference between the two groups in our study may be because there were diabetes patients included in this study. Since Lamb et al.[25] demonstrated that plasma glucose had a significantly positive correlation with D/D_0 glucose, plasma glucose level while performing the PET test may be a confounding factor.

For a 4-hour ultrafiltration volume, our study reported that there was a significantly higher volume in the sulodexide group when compared to the placebo group. The same result was also reported in an animal model study.[17] However, there are clinical studies that found no significant difference in ultrafiltration volume, which might be because of the difference in research design as mentioned above.[20, 21] Ultrafiltration volume is affected by peritoneal transport function, thus, higher ultrafiltration volume in the sulodexide group was the result of better peritoneal membrane transport status. The increase in D/P creatinine and decrease in D/D_0 glucose indicate that waste toxins pass quickly, classified this type as high transporter. This type will have poor water removal because the water and glucose from the dialysate fluid are absorbed into the body too early and cannot maintain the osmotic gradient.[6]

PD solution is one major factor of peritoneal membrane change. Characteristics of PD solution which has high concentration of glucose and lactate contributes to peritoneal membrane remodeling and functional change. This factor was controlled by using conventional PD solution in all patients. Besides, no difference in baseline PD regimen between two groups was found in this study, average number of cycles was 4 dwells per day and PD dose was 8 liters per day which is a standard regimen.

This study showed the tendency of sulodexide in preserving peritoneal membrane function. Because the mechanism of sulodexide is involved in the inhibition of matrix synthesis and angiogenesis, the permeability of small solutes including creatinine and glucose will consequently decrease and leads to the increase in ultrafiltration volume. Overall, it results in the reduction of volume and uremic toxins retentions.

Conclusion

Our data suggest that the administration of sulodexide has a potentially beneficial effect in the prevention of peritoneal membrane damage in PD patients. Sulodexide may be used to slow the progression of peritoneal membrane change.

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