Paricalcitol Protects Peritoneal Membrane Function in Encapsulating Peritoneal Sclerosis

Parikalsitol Enkapsüle Peritoneal Sklerozisde Peritoneal Membran Fonksiyonlarını Korur

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ABSTRACT

OBJECTIVE: The most lethal complication of peritoneal dialysis is encapsulating peritoneal sclerosis (EPS), which develops as a result of epithelio-mesenchymal transformation (EMT) and known fibrotic processes. Paricalcitol has previously been shown to inhibit both EMT and fibrosis. We investigated the effect of paricalcitol on EPS.

MATERIAL and METHODS: Forty non-uremic albino Wistar rats divided into four groups of equal numbers. The first group was administered 2 mL saline intraperitoneally (IP) and the second group was administered 2 mL of 200 gram chlorhexidine gluconate (CG) (0.1%) dissolved in saline and ethanol (15%) IP. The treatment groups received CG for three weeks in addition to subcutaneous paricalcitol at a dose of 0.2 mcg/kg/day to the third group and 0.4 mcg/kg/day to the fourth group. A one-hour peritoneal equilibration test was performed with 25 mL 3.86% PD solution at the end of the study. Peritoneal membrane and intracardiac blood samples were obtained.

RESULTS: D/P urea was significantly low in both treatment groups when compared to group 2 ($p<0.05$). Paricalcitol co-treatment recovered ultrafitration failure and peritoneal membrane thickness was better paricalcitol groups but there was no statistically significant difference between the groups. Serum calcium, phosphorus and parathyroid hormone levels were similar in all groups.

CONCLUSION: Paricalcitol can be effective in the protection of peritoneal functions.

KEY WORDS: Paricalcitol, Encapsulating peritoneal sclerosis, Peritoneal membrane permeability, Ultrafiltration failure, Peritoneal membrane function

ÖZ

AMAÇ: Periton diyalizinin en öldürücü komplikasyonu olan enkapsüle peritoneal sklerozis (EPS), epithelio-mezenkimal dönüşüm (EMT) ve bilinen fibrotik süreçlerinin bir sonucunda meydana gelir. Parikalsitolün EMT' yi engellediği ve antifibrotik özelliklerinin olduğu gösterilmiştir. Çalışmanın amacı, deneysel EPS modeli üzerinde parikalsitolün etkisini araştırmaktır.

GEREÇ ve YÖNTEMLER: Kırk adet üremik olmayan 200-220 gram ağırlığında, albino wistar cinsi, dişi sıçan kullanıldı. Sıçanlar rastgele eşit sayıda dört gruba ayrıldı. Üç hafta süreyle birinci gruba intraperitoneal (İP) 2 mL serum fizyolojik verildi, ikinci gruba 2 mL/ 200 gram serum fizyolojik içinde çözünmüş klorheksidin glükonat (KG) (%0,1) ve etanol (%15) İP verildi. Üçüncü ve dördüncü gruba üç hafta boyunca KG ile birlikte sırasıyla 0,2 mcg/kg/gün ve 0,4 mcg/kg/gün derialtı parikalsitol yapıldı. Çalışma sonunda, tüm gruplara 1 saatlik 25mL %3,86 PD solüsyonu ile periton eşitleme testi yapıldı. Peritoneal sıvı, intrakardiyak kan örnekleri elde edildi ve patolojik inceleme için peritonun İP uygulama yapılmayan tarafı alındı. TGF-β1 düzeyi periton sıvısından çalışıldı.

BULGULAR: D/P üre parikalsitol alan gruplarda grup 2 ile karşılaştırıldığında belirgin olarak daha düşüktü ($p<0,05$). Parikalsitol tedavisi doz bağımlı olarak ultrafiltrasyon kaybını azalttı, aynı zamanda parikalsitol alan sıçanlarda periton kalınlığı daha azdı. Ancak bu iki bulguda istatiksel olarak anlamlılığa ulaşmadı. Serum kalsiyum, fosfor ve parathormon değerleri tüm gruplarda benzerdi.

SONUÇ: Parikalsitol peritoneal membran fonksiyonlarının korunmasında etkili olabilir.

ANAHTAR SÖZCÜKLER: Parikalsitol, Enkapsüle peritoneal sklerozis, Peritoneal membran geçirgenliği, Ultrafiltrasyon kaybı, Peritoneal membran fonksiyonları

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INTRODUCTION

Peritoneal dialysis (PD) is a renal replacement treatment that is commonly used worldwide. The peritoneal membrane is subject to many non-physiological factors (non-biocompatible peritoneal dialysis solutions, peritonitis episodes etc.) during PD use. Structural and functional changes occur as a result of this exposure and the most lethal and severe change is encapsulating peritoneal sclerosis (EPS). The underlying pathophysiological reasons of EPS are inflammation, epithelio-mesenchymal transformation (EMT) and fibrosis. The active pathological process here is similar to the other inflammatory and fibrotic processes. Mediators such as transforming growth factor 1 (TGF 1), vascular endothelial growth factor, interleukin-6, matrix metalloproteinase and plasminogen activator inhibitor type 1 play a central role (1). EPS has no known treatment for this reason any intervention that can block fibrosis may increase the usage duration of the peritoneal membrane and prevent mortality.

Calcitriol deficiency emerging during chronic kidney disease (CKD) is a condition that affects mortality independently of PTH and phosphorus (2). Paricalcitol is a vitamin D analogue and is used in the treatment of the calcitriol deficiency that develops during CKD. There has currently been an increase in the number of studies reporting that paricalcitol has nephroprotective and antifibrotic effects and is not just a vitamin D replacement treatment. Paricalcitol has been shown to decrease the kidney damage developing due to cyclosporine (3) in addition to an anti-proteinuric effect in patients with chronic kidney failure (4). Vitamin D analogues are also negative endocrine regulators of renin-angiotensin-aldosterone (RAS) (5). RAS blockers have previously been shown to block EPS (6, 7). These mechanisms can be some of the reasons for their antifibrotic and anti-hypertensive effects (5, 8). Paricalcitol has been shown to prevent progression in the experimental kidney failure model by suppressing the angiotensin gene in the kidney (9). When paricalcitol was used with trandolapril, a RAS blocker, it blocked fibrosis by showing an additive effect as well as providing renal protection by decreasing the secondary renin increase caused by trandolapril (10). It has also been shown to inhibit fibrosis in obstructive nephropathy and inhibit EMT in renal tubular cells (11). Paricalcitol has been reported to block EMT, a key mechanism of peritoneal fibrosis, in two important recent studies (12, 13).

The aim of this study was to investigate the effectiveness of paricalcitol, with a proven effect on inflammation, EMT and the fibrosis process, on preventing EPS, one of the most lethal complications of peritoneal dialysis that can also emerge after similar processes.

MATERIAL and METHODS

Forty-two female non-uremic Wistar albino rats kept in polycarbonate cages at 24 °C constant room temperature with 12 hours of light and 12 hours of dark periods were included in the study. Rats were fed with a standard laboratory diet without water restriction and were randomized into four groups.

Experimental EPS was created in rats with the administration a solution containing 0.1% chlorhexidine gluconate (CG) (Hibiscrub® 500 mL 4% solution Astra Zeneca-Abdi İbrahim, Istanbul, Turkey) dissolved in isotonic saline and 15% ethanol through the intraperitoneal (IP) route for three weeks (6, 7, 14).

The first group was accepted as the control group and 2 mL isotonic saline was administered to this group IP every day during the study. The second group (CG group) was administered 2 mL CG solution daily for 3 weeks IP. The third group was administered 2 mL CG solution daily for 3 weeks IP with 0.2 mcg/kg/day paricalcitol (Zemplar® 5 mcg/mL ampoule, Abbott) subcutaneously (SC). The fourth group was administered 2 mL CG solution daily for 3 weeks IP with 0.4 mcg/kg/day paricalcitol subcutaneously (SC).

A one-hour PET test was performed at the end of the study. 25 mL PD solution containing 3.86% glucose (Dianeal 3.86% Eczacıbaşı-Baxter, İstanbul, Turkey) was heated to 37°C for the test. It was then injected to the peritoneal cavity with a 22 gauge needle. The rats were allowed to move freely after the injection. The abdomen was entered with a midline abdomen incision under ether anesthesia one hour later. Intraabdominal fluid was aspirated without leakage. The volume of the aspirated fluid was recorded. Peritoneal samples were taken from a region far away from the injection site. Blood samples were taken with cardiac puncture.

Blood and dialysate urea, creatinine, glucose, calcium (Ca), phosphor (P) and parathormone (PTH) levels were studied with commercial kits on an autoanalyzer (Abbott Architect c8000 autoanalyzer and Abbott Architect i2000 autoanalyzer, respectively). Net UF was calculated as the difference of the fluid administered and removed from the peritoneum.

The dialysate TGF-β1 level was determined using commercial rat ELISA kits (Invitrogen Corporation, Camarillo, CA 93012, catalogue no: KAC1688).

Peritoneal samples were taken from the non-injected right quadrant of the abdomen. A layer 1 cm in length and 3 mm in thickness was removed from the abdomen front wall midline and the right half perpendicular to it except for the skin. Peritoneal membrane samples were fixed with 4% formalin. These were embedded in paraffin. Profiles of 5 micron thickness were taken and stained with the hematoxylin-eosin and Masson trichrome stains. All samples were evaluated by the same pathologist without knowing which group they belonged to. Peritoneal thickness, neovascularization, inflammation and fibroblastic activity were examined. Peritoneal thickness was evaluated with an ocular micrometer and the counts of new vessel formation, mononuclear cells and fibroblasts were evaluated at 400X magnification.

The SPSS 20.0 software was used for statistical analysis. The Kruskal-Wallis test and, in case of significance, the Mann-Whitney-U test were used for the comparison of two groups. p <0.05 was accepted as the limit of significance. The results were presented as mean ± standard error of the mean (SEM).

Approval was obtained from Uludag University Faculty of Medicine's Animal Experiments Local Ethics Committee for this study. The study experimental procedures were in compliance with the Guide for the Care and Use of Laboratory Animals.

RESULTS

According to our results, peritoneal membrane functions were protected by the paricalcitol. D/P urea levels in the CG group were significantly higher than in the control group (0.71±0.08 vs 0.49±0.05, respectively; p<0.05). D/P levels in the groups receiving 0.2 and 0.4 mcg paricalcitol (0.42±0.05 and 0.42±0.02, respectively) were significantly lower than in the CG group (0.71±0.08) (p<0.05). When the control group and the treatment groups were compared, no significant difference was present between the D/P levels (Figure 1C). D_1/D_0 glucose, another peritoneal function indicator, was significantly lower in the CG group than the control group (0.14 ± 0.01 vs. 0.29 ± 0.03, respectively; p<0.05). In the treatment groups, the D_1/Do level was only preserved in the group receiving 0.4 mcg paricalcitol (0.24 ± 0.02) and was significantly higher than in the group receiving 0.2 mcg paricalcitol (0.13 ± 0.02) and the CG group (0.14 ± 0.01) (p<0.05, Figure 1D).

Paricalcitriol was able to achieve the recovery of UF failure in terms of ultrafiltration deficiency. UF volumes in the CG group had deteriorated significantly when compared with the control group (6.30 ± 1.55 vs 2.00 ± 1.66, respectively). 0.4 mcg paricalcitol had led to a significant recovery of UF loss when compared to the CG group but this effect did not reach significance (p>0.05) (Figure 1B).

Structural change (peritoneal thickness, number of vessels and fibroblasts) results were better in the treatment groups than the CG group. The number of fibroblasts in the 0.4 mcg paricalcitol group was significantly lower than in the CG group (1.98 ± 0.25 vs. 4.32 ± 0.44, respectively; p<0.05, Table I). The peritoneal thickness had increased in the CG group when compared to the control group (103 ± 12.21 μm vs. 25.32 ± 4.28 μm, respectively; p<0.05). Peritoneal thickness gradually decreased in the treatment groups and paricalcitol had beneficial effect but did not reach significance (Figure 1A,E).

The TGF-β1 level was so low that it could not be measured in the peritoneal fluid of the control group. TGF-β1 levels in groups treated with paricalcitol were similar to the CG group (Table I).

No statistically significant difference was found in the parameters when serum values were investigated. Although the parathormone levels in the treatment groups were lower than the control and the CG group, no statistically significant difference was present. The Ca and P levels again did not show a difference between the treatment groups and other groups (Table I).

DISCUSSION

The results of our study showed that paricalcitol, which is a vitamin D analogue, provided significant protection of peritoneal functions in the EPS model. Improvement of ultrafiltration volume and decrement of peritoneal membrane thickness, which are indicators of peritoneal fibrosis, were provided by paricalcitriol in dose-dependent manner. However, these were not statistically significant. The most important factor limiting peritoneal dialysis is peritoneal fibrosis and the loss of ultrafiltration. EPS is the most lethal long-term complication. It emerges as a result of mesenchymal transformation of peritoneal mesothelial cells and the fibrotic process as a result of the factors irritating the peritoneal membrane. Ultrafiltration failure and peritoneal fibrosis occur as a result.

Table I: Laboratory findings.

	Control	CG	CG+Pari 0.2 mcg	CG+Pari 0.4 mcg
Parathyroid hormone (pg/dL)	1.74 ± 0.57	1.51 ± 0.28	0.79 ± 0.10	0.74 ± 0.25
Phosphorus (mg/dL)	7.45 ± 0.29	7.10 ± 0.30	7.5 ± 0.27	7.2 ± 0.27
Calcium (mg/dL)	10.34 ± 0.40	10.18 ± 0.21	10.18 ± 0.26	11.05 ± 0.50
CaxP product (mg^2/dL^2)	77.15 ± 4.58	72.44 ± 3.99	76.92 ± 4.80	80.27 ± 6.28
TGF-β1 (pg/mL)*	Not determine	75.56 ± 24.89	19.82 ± 9.74	49.04 ± 19.42

Data are means ± **SEM** of ten animals per group (n=10). There were no significant differences between groups in terms of laboratory findings.

*Peritoneal fluid TGF-β1 was determined. Control group = 2 mL isotonic saline daily intraperitoneal (IP) injection for 3 weeks; CG group = IP injection of 2 mL/200 g chlorhexidine gluconate (CG) (0.1%) and ethanol (15%) dissolved in saline, daily for 3 weeks; Paricalcitol 0.2 group = daily IP injection CG (0 – 3 weeks) + 0.2mcg/kg paricalcitol, subcutaneously, daily for 3 weeks; Paricalcitol 0.4 group = daily IP injection CG (0 – 3 weeks) + 0.4 mcg/kg paricalcitol, subcutaneously, daily for 3 weeks.

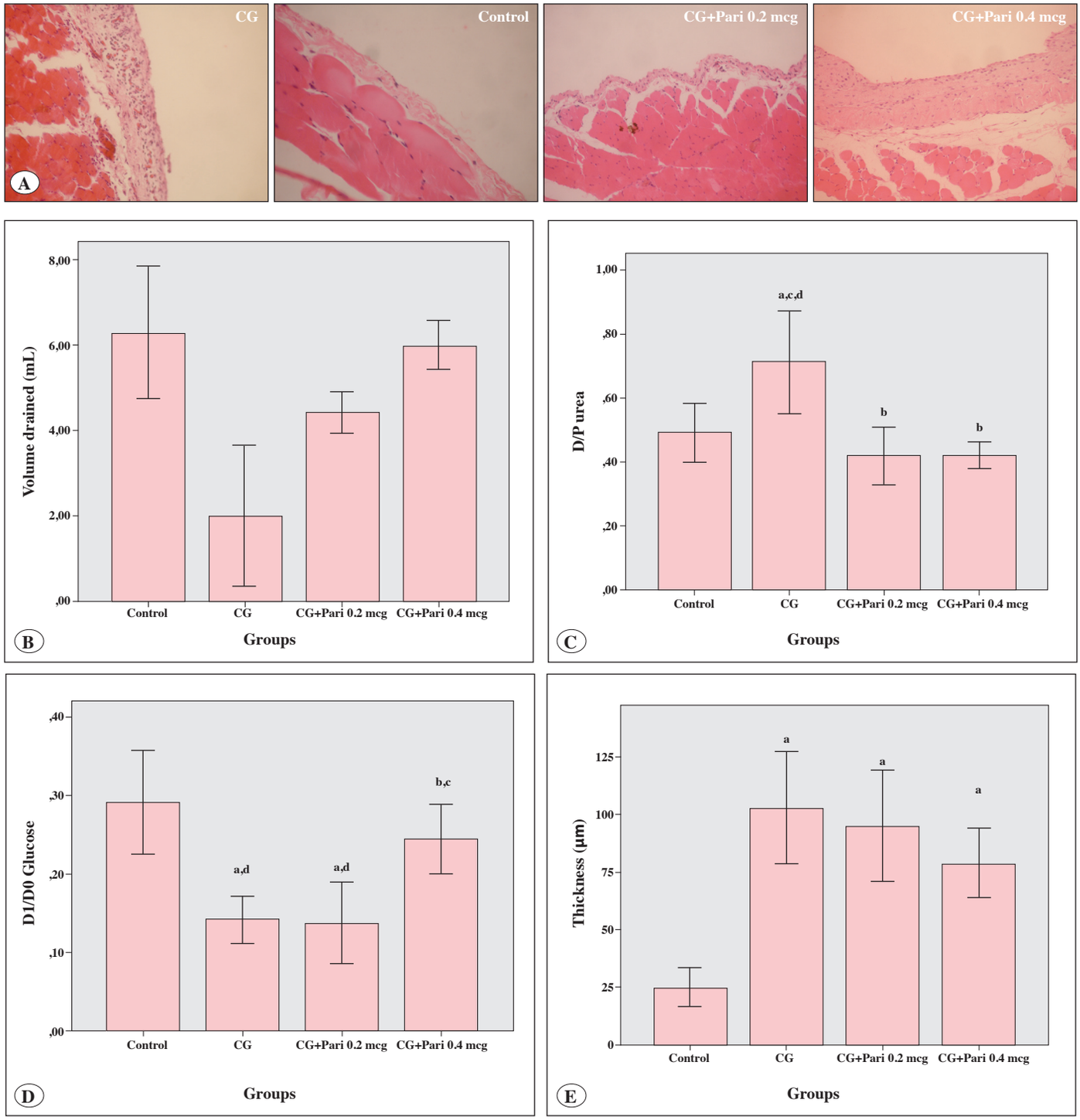

Figure 1: *Effects of paricalcitol therapy on peritoneal permeability and functional parameters. **A)** Paraffin sections of the peritoneal membrane from the 4 groups were stained with haematoxylin eosin. **B)** Peritoneal permeability was determined by net ultrafiltration. **C and D)** Graphic presentation showed paricalcitol protect peritoneal function parameters. **E)** Paricalcitol showed beneficial effect on peritoneal membrane thickness but the effect did not reach statistical significance.*

CG: *Chlorhexidine gluconate,* ***Pari:*** *Paricalcitol,* ***D/P Urea:*** *dialysate-to-plasma ratio of urea,* ***D/D0 glucose****: Where D is glucose concentration in the dialysate and D0 is glucose concentration in the dialysis solution before it is infused into the peritoneal cavity.*

[a]: p< 0.05, group versus control, [b]: p< 0.05 group versus CG, [c]: p< 0.05 group versus Paricalcitol 0.2, [d]: p< 0.05 group versus Paricalcitol 0.4.

Paricalcitol may decrease peritoneal fibrosis with its effects on the main mediators of EMT. Tan et al. (11) have demonstrated that paricalcitol prevents the fibrosis that occurs following unilateral ureteral obstruction (UUO) and that it could preserve tubular epithelial integrity by preventing EMT in tubular cells in their study where they evaluated the effects of paricalcitol on renal interstitial fibrosis by creating renal tubular fibrosis through UUO. Paricalcitol produced this effect by decreasing both the TGF-β1 level and its receptor expression. Kang et al. (12) showed that paricalcitol decreased TGF-β1 mediated Smad phosphorylation in human peritoneal mesothelial cells (HPMCs) cultured with TGF-β1 in their recent *in vivo* study. They divided 42 rats into 3 groups as control, those receiving PD and those receiving paricalcitol together with PD in the in-vitro arm of the same 8-week study. The peritoneal thickness was significantly greater in the groups administered PD when compared with the control group. Paricalcitol co-treatment significantly decreased the peritoneal thickness. The interstitial extracellular matrix accumulation was also significantly reduced by treatment with paricalcitol. Gonzalez-Mateo et al. (13) similarly showed that paricalcitol co-treatment significantly decreased peritoneal membrane thickness in rats that had undergone peritoneal dialysis. We found a correlation between increasing doses of paricalcitol co-treatment and decreased peritoneal membrane thickness. However, this did not have statistical significance. The most important reason may be that our experimental protocols were different. Our model was an EPS model and the agents (CG and alcohol) we used to create fibrosis were quite potent when compared with PDF containing 4.25% glucose used in the other two studies. This may be why the positive effect on peritoneal membrane thickness did not reach statistical significance in our study.

Similarly, the TGF-β1 levels tested from peritoneal fluid in our study decreased with paricalcitol co-treatment but this decrease was not statistically significant. Gonzalez-Mateo et al. (13) did not find a significant increase in peritoneal fluid TGF-β, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-10, IFN-γ and TNF-α levels similar to our study when they evaluated the effect of paricalcitol on the fibrotic process in mice which undergoing peritoneal dialysis. They only found a statistically significant difference in IL-17 levels as paricalcitol reduced the IL-17 level in peritoneal fluid. Gonzalez-Mateo et al. (13) suggested at the end of the study that TGF-β was regulated by IL-17 and may be a target for blocking fibrosis.

Peritoneal functions were significantly deteriorated together with the morphological characteristics of the peritoneum in the CG group. The most important results in our study were the D/P urea ratio, which is one of the most important indicators of peritoneal function, being protected in the treatment group and D_1/D_0 glucose ratio being significantly protected only in the group receiving a high dose (0.4 mcg/kg/day). These findings were consistent with previous studies. Kang et al. (12) found no significant improvement following co-treatment with paricalcitol in the D/P Creatinine ratio, which is an indicator of peritoneal membrane function, in the *in vivo* arm of their study. However, the glucose mass transfer value increased significantly in the PD group when compared with the initial values but did not change in the paricalcitol group. The authors did not evaluate the effects of ultrafiltration in this study. Gonzalez-Mateo et al. (13) showed that a significant level of ultrafiltration loss was experienced in the group receiving PD only compared to the group receiving paricalcitol co-treatment. However, the authors did not evaluate the permeability parameters of the peritoneal membrane in this study either. The most important limiting factor of PD is ultrafiltration loss and the marked increase in peritoneal permeability. The most important reason is exposure of the peritoneal membrane to non-physiological factors and the inflammation and fibrosis developing as a result. Paricalcitol blocking the fibrotic process and protecting ultrafiltration is a significant finding. These effects were dose related in our study. Similarly, Tan et al. (11) showed that the interstitial fibrosis decreasing effect of paricalcitol was dose dependent and reported that 0.3 mcg/kg/day paricalcitol was more effective than a dose of 0.1 mcg/kg/day.

The antifibrotic effects of RAS blocker agents are well known. One of the most important features of vitamin D receptor (VDR) agonists is their behaving like a RAS blocker and also suppressing the renin angiotensin gene expression (5, 8, 9). Li et al. (5) found that VDR -/- rats have increased renin expression and plasma angiotensin production. These rats were hypertensive and showed abnormal drinking. In this study renin mRNA expression was suppressed in a dose dependent manner after $1.25(OH)_2D_3$ treatment. Paricalcitol as a VDR agonist had an additive effect and decreased renal scarring in the nephropathy model created with UUO (10). RAS blockage was previously used in the EPS model created with chlorhexidine, which is the model we used in our study, and was found to result in significant prevention of peritoneal fibrosis as well as preservation of peritoneal functions (6, 7, 15). Behaving as a RAS blocker may have a role in the effective TGF-β1 suppression and anti-fibrotic effects of paricalcitol.

Paricalcitol could increase VDR expression in fibrotic tissue. Loss of VDR would lead to an eradication of vitamin D signaling, even when no reduction in active vitamin D levels occurs. Tan et al. (11) showed that VDR was almost completely lost in rats (95% on quantitative western blot analysis) where interstitial fibrosis was created by UUO, compared with the sham control group. However, impressively, VDR was preserved almost completely and dose dependently in the UUO + paricalcitol co-treatment group. In this study, the authors suggest that VDR can also mediate multiple cross-talks and integrate diverse signaling inputs by virtue of its ability to interaction with other transcription regulators such as Smad 3 and β-catenin. The loss would therefore not only obliterate vitamin D signaling but also

disrupt the homeostasis of other important signaling networks, leading to a disparaging consequence. The protection of VDR receptors and RAS blockage may have a role in the effect of paricalcitol in decreasing the fibrosis and protecting peritoneal functions and this effect is dose-dependent as we observed in our study.

One of the important findings of our study was a decrease in the number of fibroblasts in the peritoneal area in the group receiving high dose paricalcitol. Fibroblasts transform to myofibroblasts during the EMT process and play a major role in the development of peritoneal fibrosis (16).

No significant difference was found serum levels of PTH, Ca, P and CaXP product between the groups receiving paricalcitol and the other groups. The expected hypercalcemia, hyperphosphatemia and PTH oversuppression effects were not observed. Tan et al. (11) did not find any difference in PTH, Ca and P levels in mice receiving paricalcitol in their study, parallel to our findings. One reason is that paricalcitol, a new VDR agonist, affects the bowels less (17), and another reason may be the fact that we did not create a uremic environment in our study protocol. Because of this reason the functioning kidneys may have dealt with the Ca and P overload.

CONCLUSION

Paricalcitol protected ultrafiltration and peritoneal functions dose dependently in the experimental EPS model we created. The useful duration of the peritoneal membrane may be extended with this beneficial effect of paricalcitol in patients undergoing PD.

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COMPLIANCE WITH ETHICAL STANDARDS

The authors declare no conflict of interest.

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Ethical approval was obtained from Uludag University Faculty of Medicine's Animal Experiments Local Ethics Committee and all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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