

Peritoneal Dialysis Patients with High Effluent Fibrin Degradation Products

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Encapsulating peritoneal sclerosis (EPS) is a major and fatal complication of peritoneal dialysis (PD). For treatment, the efficacies of steroids, tamoxifen, immunosuppressants, and surgical total intestinal enterolysis have been reported, but the results have not been sufficient. Because treatment after the onset of EPS is limited, a prophylactic therapy is needed. We previously reported that the level of effluent fibrin degradation products (eFDPs) is predictive of EPS. In the present study, we investigated the clinical course of PD cases with high eFDP levels, and the effect of prophylactic steroid therapy against EPS.

Between January 2002 and August 2008, we investigated 310 PD patients, of whom 22 had an eFDP level of 30 $\mu\text{g}/\text{mL}$ or more in 4-hour effluent from a fast peritoneal equilibration test (PET). Mean patient age was 62.6 ± 11.1 years, and mean duration of dialysis was 42.7 ± 45.5 months (range: 1 – 202 months). During a fast PET performed every 6 months, we measured, in 4-hour effluent, eFDPs, cancer antigen 125 (eCA125), and dialysate-to-plasma creatinine (D/P Cr). In addition, we calculated D/P β_2 -microglobulin ($\beta_2\text{MG}$) from levels in overnight dialysis effluent and blood.

In the 22 cases, the mean eFDP level was 66.6 ± 39.2 $\mu\text{g}/\text{mL}$; the D/P Cr, 0.78 ± 0.1 ; and the D/P $\beta_2\text{MG}$, 0.45 ± 0.2 . Steroid (5 – 30 mg daily) was administered to 8 of the 22 patients. In the 8 treated cases, the eFDP level, the D/P Cr, and the D/P $\beta_2\text{MG}$ declined, but did not return to normal, and EPS developed in 2 patients. The eFDP level was high when dialysis was introduced, but returned to normal in 2 of the remaining 14 patients. In 1 of the 14 cases, peritonitis developed 5 times, followed by rapid elevation in the eFDP level. The patient with this intractable peritonitis was switched to hemodialysis. The other 11 patients received no steroid therapy. In 1 of these 11 patients, the eFDP level declined, but not in the others.

We suggest that active steroid therapy for patients with a high level of eFDPs may prevent EPS development.

Key words

Fibrin degradation products, encapsulating peritoneal sclerosis, prophylactic therapy

Introduction

Peritoneal dialysis is widely applied, as is hemodialysis, as an established treatment for end-stage renal failure. However, the penetration of peritoneal dialysis has recently been declining, and one reason may be encapsulating peritoneal sclerosis (EPS). The clinical and histologic features of EPS have been clarified by many clinical and basic studies, and the efficacies of treatments using steroids, tamoxifen, and surgical dissection of intestinal adhesions have been reported, but EPS remains the most serious fatal complication of peritoneal dialysis (1). At the onset of EPS, irreversible intestinal changes for which drug therapy is limited are complete. To avoid EPS, a prophylactic therapy is needed.

We previously reported that fibrin degradation products in peritoneal dialysis effluent (eFDPs) reflect the peritoneal inflammatory state and intestinal fibrin capsule formation (a histologic characteristic of EPS) and are a useful factor in predicting EPS (2). In the present study, we investigated the clinical characteristics of cases with a high eFDP level, and the efficacy of steroid therapy in such cases.

Patients and methods

Between January 2002 and August 2008, we investigated 310 PD patients, of whom 22 had an eFDP level of 30 $\mu\text{g}/\text{mL}$ or more in 4-hour effluent on a fast peritoneal equilibration test (PET). Mean patient age was 62.6 ± 11.1 years, and mean duration of dialysis was 42.7 ± 45.5 months (range: 1 – 202 months). During a fast PET performed every 6 months, we measured, in 4-hour effluent, eFDPs, cancer antigen 125 (eCA125),

and dialysate-to-plasma creatinine (D/P Cr). In addition, we calculated D/P β_2 -microglobulin (β_2 MG) from levels in overnight dialysis effluent and blood.

Results

In the 22 patients with an eFDP level of 30 μ g/mL or higher, the mean eFDP level was 66.6 ± 39.2 μ g/mL; mean D/P Cr, 0.78 ± 0.1 ; mean D/P β_2 MG, 0.45 ± 0.2 ; and mean eCA125, 31.9 ± 12.9 U/mL. One of the 22 patients developed 5 peritonitis episodes, and 4 patients were treated with icodextrin-based peritoneal dialysate.

A steroid was administered at a mean dose of 15.6 ± 8.2 mg daily, with 5–30 mg daily as the initial dose, to 8 of the 22 patients. The mean duration of dialysis in the 8 patients was long: 205.5 ± 15.5 months as compared with 71 ± 63.5 months for the group of 22. In 2 of the patients, peritonitis had previously developed, and icodextrin-based peritoneal dialysate was used for 2 patients. Steroid administration led to a decline in the mean eFDP level to 8.9 ± 10.1 mg/mL from 75.5 ± 39 mg/mL, in the mean D/P Cr to 0.63 ± 0.1 from 0.83 ± 0.08 , and in the mean D/P β_2 MG to 0.33 ± 0.19 from 0.54 ± 0.22 , but the eCA125 level was unchanged. In 2 of the 8 cases, the eFDPs, D/P Cr, and D/P β_2 MG declined, but did not return to normal, and both cases developed EPS (Table I, Figure 1).

In one of the EPS cases, a high eFDP level persisted for a prolonged period and then further increased sharply, and a steroid was administered after the sharp increase. The eFDP level declined, but did

not return to normal. In the other case, the eFDP level increased rapidly after treatment with icodextrin-based peritoneal dialysate, and EPS developed. The eFDP level declined with steroid treatment, but it did not return to normal. In both of these patients, EPS was treated with PD withdrawal and total intestinal enterolysis.

The other 14 patients received no steroids. In 11 of the 14, the duration of dialysis was 33 ± 20.4 months; the eFDP level, 31.3 ± 1.3 μ g/mL; the D/P Cr, 0.73 ± 0.12 ; the D/P β_2 MG, 0.34 ± 0.15 ; and the eCA125 level, 33.4 ± 16.2 U/mL. In 10 of these 11 patients, the eFDP level, D/P Cr, and D/P β_2 MG did not change. In 2 of the 14 patients, icodextrin-based peritoneal dialysate had been used since the introduction of dialysis. The eFDP level was high immediately after the introduction of dialysis and declined thereafter. In 1 patient, the eFDP level increased rapidly after 5 episodes of peritonitis, and this intractable peritonitis led to the patient being switched to hemodialysis.

Discussion

Encapsulating peritoneal sclerosis is the major fatal complication of peritoneal dialysis. The incidence is reportedly 2.5%, but it increases with duration of peritoneal dialysis, and the mortality rate is high (1). The main causes are long-term exposure to bioincompatible dialysate and peritonitis. Treatments including steroids, tamoxifen, immunosuppressants, and surgical total intestinal enterolysis have been

TABLE I Outcome of steroid therapy in the 8 treated patients

Patient	Initial dose of steroid ^a (mg/day)	eFDP (μ g/mL)		D/P Cr		D/P β_2 M		eCA125 (U/mL)		Outcome
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	20	137.9	19.9	0.93	0.78	0.52		23	19.9	EPS
2	30	35.8	28.4	0.9	0.71	0.26	0.16	27	26	EPS
3	10	91.6	1.7	0.84	0.57	0.84	0.22	36	17	PD+HD
4	5	30.4	4.8	0.72	0.62	0.72	0.63	41	33	PD
5	10	111.9	0.3	0.82	0.47	0.8	0.47	26	108	PD+HD
6	20	44.3	1	0.89	0.74	0.4	0.46	24	63	PD+HD
7	10	93.3	5.7	0.74	0.55	0.39	0.16	29	20	PD+HD
8	20	58.5	9.3	0.78	0.65	0.36	0.21	29	30	PD+HD
Mean \pm SD	15.6 \pm 8.2	75.5 \pm 39	8.9 \pm 10.1	0.83 \pm 0.08	0.63 \pm 0.1	0.54 \pm 0.22	0.33 \pm 0.19	29.4 \pm 6.2	39.6 \pm 31.2	

^a Steroid administration led to a decline in the eFDP level in all cases. In 2 of the 8 cases, eFDP did not return to normal, and both patients developed EPS.

eFDP = effluent fibrin degradation products; D/P Cr = dialysate-to-plasma ratio of creatinine; D/P β_2 M = dialysate-to-plasma ratio of β_2 -microglobulin; eCA125 = effluent cancer antigen 125; EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis; HD = hemodialysis; SD = standard deviation.

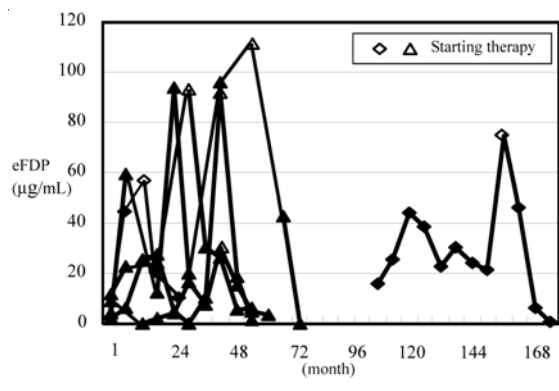


FIGURE 1 The 6 cases of effective steroid therapy. The effluent level of fibrin degradation products (eFDP) was moderate, and steroid therapy was rapidly started, which led to a decline in eFDPs and prevented development of encapsulating peritoneal sclerosis.

reported. Steroids, tamoxifen, and immunosuppressants are administered for early-stage EPS. Steroids have been reported to be effective in 15 of 39 cases (38.5%) (1). In 17 and 24 cases treated with tamoxifen and immunosuppressants respectively, the median survival times were 15 months and 12 months (2), showing that the effects were insufficient. In contrast, the survival rate following surgical total intestinal enterolysis for late-stage EPS is as high as 93.1%, but the recurrence rate is 25.4% (1). The condition remains intractable, with a high mortality, and the effects of current treatments for EPS are limited after onset of the condition. Accordingly, a prophylactic therapy is needed.

Bioincompatible dialysis solutions cause low-grade peritoneal serositis, which increases the transfer of coagulation factors into the peritoneal cavity, resulting in a hypercoagulable state and leading to fibrin generation with increased fibrinolysis—that is, a high-FDP state (3–5). Previously, we reported that the level of eFDPs reflects the peritoneal inflammatory state and intestinal fibrin capsule formation, making it a useful factor for predicting EPS (6). During serial PET measurements, the level of eFDPs increased in correlation with D/P Cr, but increased sharply in some cases. We speculated that steroid treatment during this period of excess eFDPs might prevent the development of EPS.

We investigated the clinical course of patients who had a high eFDP level and who received therapeutic

steroids. A steroid was administered to 8 of the 22 patients with an eFDP level of 30 µg/mL or higher, and the eFDP level and the D/P Cr declined in all cases. However, 2 of these patients developed EPS. Because one of the patients was undergoing long-term peritoneal dialysis and was showing a persistently high FDP level in effluent, we speculate that capsule formation had already occurred. In another case, the eFDP level increased rapidly after the use of icodextrin-based peritoneal dialysate; EPS development followed. In this latter case, icodextrin-induced inflammation persisted (7,8). In the other 6 cases, although the duration of PD was long, elevation in the eFDP level was moderate, and a steroid was rapidly administered, which led to a reduced eFDP level and prevented EPS development.

The remaining 14 cases were not treated with steroids. Their duration of dialysis was relative short, and their eFDP levels were lower than those of the patients who received steroid therapy.

Conclusions

In peritoneal dialysis patients with a high eFDP level, steroid therapy effectively led to a decline in eFDPs. We suggest that peritoneal dialysis patients with an eFDP level above 40 µg/mL should receive steroid therapy. Such steroid therapy may prevent EPS development, but a therapeutic effect cannot be expected in cases in which a high eFDP level has persisted for a prolonged period followed by a further increase. Thus, steroids should be administered in the earliest phase of elevation in the eFDP level. Further work is needed to determine the optimal dose of steroid.

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