Hormone Replacement Therapy plus Pelvic Floor Muscle Exercise for Postmenopausal Stress Incontinence

A Randomized, Controlled Trial

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OBJECTIVE: To investigate the effects of the combination of pelvic floor muscle exercise (PFME) and estriol on postmenopausal stress incontinence (SI).

STUDY DESIGN: Sixty-six patients with postmenopausal SI were randomized to a group treated with a combination of estriol (1 mg/d) and PFME (group A, n = 32) and a group treated with PFME alone (group B, n = 34). Efficacy was evaluated every three months based on stress scores obtained from a urinary incontinence (UI) questionnaire.

RESULTS: A significant decrease in stress score was observed in mild and moderate UI patients in both groups three months after the commencement of therapy (A and B, P < .0001). The therapeutic effect in group A was more prominent for up to 18 months in mild UI and for up to 12 months in moderate UI (A vs. B, P < .05). Kaplan-Meier analysis showed that the cumulative morbidity rate in mild SI patients was significantly lower in group A (0%) than in group B (12%, P < .005).

Combined therapy consisting of E_3 and PFME should be first-line therapy for SI.

CONCLUSION: Combination therapy with estriol plus PFME was effective and is capable of serving as first-line treatment for mild SI. (J Reprod Med 2001;46: 213–220)

Keywords: hormone replacement therapy; urinary incontinence, stress; menopause; estriol; pelvic floor muscle exercise.

Introduction

Urinary incontinence (UI) still does not occupy an important position in the field of gynecology because of poor recognition of the disease by patients and an insufficient number of specialists in the disease. The World Health Organization warns that the number of women with UI will greatly increase

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in the near future[1] and that it will be impossible for only a limited number of specialists to manage all the potential patients with UI. Consequently, it is very important for all gynecologists to be able to manage this disease in an appropriate manner. Unfortunately, however, there are many diagnostic methods, examinations and treatment methods for UI that are complicated and distressing to patients.

To solve this problem, we proposed a method of differential diagnosis and severity classification based on the score on a UI questionnaire.[2,3] The randomized, controlled study reported on below was carried out to investigate the clinical efficacy of a combination of estriol (E_3) and pelvic floor muscle exercise (PFME),[4] which has been established as a treatment method for stress incontinence (SI), a disease that tends to increase considerably with age.

Materials and Methods

Patients

Seventy-eight UI patients (aged 54–75 years) who consulted the participating institutions between April 1996 and December 1999 and were diagnosed with SI by gynecologists were included in this clinical study. The reliability of the diagnoses was increased by using a questionnaire on UI consisting of 15 items that all of the patients were required to fill out to standardize the diagnosis (Table I).[2,5]

Study Design

Before giving their consent to participate in the study, all the patients who came to the Urinary Dysfunction Clinic, Department of Obstetrics and Gynecology, Osaka City University Medical School Hospital, were given sufficient information on the significance and details of the study and the absence of any disadvantage to them if they decided not to participate in it.

The patients diagnosed as having SI by gynecologists were randomly assigned to two groups: a group treated with a combination of E_3 replacement therapy and pelvic floor muscle exercise (group A) and a group treated with PFME alone (group B). Treatment began after a one-week observation period starting on the day of the initial examination for UI at the institution. The patients returned to the hospital every three months, and changes in frequency, UI score questionnaire and patients' own detailed impressions of changes in their symptoms were recorded. The efficacy of treatment was evaluated in patients who had been treated for two years after the start of the study.

Questionnaire

A questionnaire prepared by Gaudenz in 1979 that had been partially modified to make it more suitable for a Japanese population was used in this study. It consisted of 15 questions. The answers to each question were assigned a certain number of points and, depending on the answer, included in the stress score (ss) or urge score (us). The total ss and us points were added up separately, and the diagnosis was based on the zones into which each of the scores fell. Zones a, b and c were designated SI zones; zones g, i and j, urge incontinence zones; zones e, f and h, mixed incontinence zones; and zone d, an unclassified incontinence zone (Table I, Figure 1).[2,5]

Classification of the Severity of SI

The results of our previous study on UI scores showed that an ss range of 10–17, 18–23 and 24–26 corresponded to mild, moderate and severe UI, respectively, according to the severity evaluation criteria based on the pad test, as defined by the International Continence Society (ICS).[6] Severity in this study was therefore evaluated on the basis of ss, and the patients were assigned to one of three groups—mild, moderate or severe, according to the severity of their UI.[3]

Treatment

E_3, 1-mg tablet/d, was administered as hormone replacement therapy.[7] Whenever a patient stopped taking the tablets, the reason was fully investigated. The endometrium of the uterine corpus was observed by ultrasonography (once a month) and endometrial Pap smears (every six months). Specialists in gynecology instructed the patients on PFME until they mastered the technique.[4] Each patient was also given a videotape that demonstrated the proper method of performing PFME, and the patient was instructed to perform the exercise for 15 minutes a day.

Data Analysis

The level of significance of differences between the two groups was evaluated, and the significance of differences in UI score before and after treatment within the same group was evaluated by Students' *t* test and the χ^2 test. The Kaplan-Meier method was used for analysis of the cumulative morbidity rate in SI patients after the start of treatment. A P value of $< .05$ was considered evidence of a significant difference. All data are expressed as mean ± SD.

Table I *UI Score Questionnaire*

Question	SS	US
1. How often do you experience urine leakage?		
1. Rarely	1	
2. Sometimes	1	
3. Every day, many times a day		1
4. Constantly		1
2. On what occasions have you experienced urine leakage?		
1. When coughing or sneezing	1	
2. When sitting or lying down		1
3. How much urine leaked?		
1. Only a few drops to a small amount	1	
2. A considerable amount		1
4. At what intervals do you go to the toilet to urinate every day?		
1. At 3–6-hour intervals	3	
2. At 1–2-hour intervals		2
5. Do you go to the toilet to urinate after falling asleep at night?		
1. Never or once a night	3	
2. More than once a night or many times a night		3
6. Do you ever experience urine leakage when sleeping at night?		
1. Never	1	
2. Often		1
7. When you feel urinary urgency, can you control it?		
1. Yes, I can.	3	
2. Unless I go to the toilet soon (in 10–20 minutes), I leak urine.	2	
3. I cannot control it, and I leak urine.		3
8. Do you ever leak urine on the way to the toilet?		
1. Never, or rarely	3	
2. Almost always		3
9. Do you ever leak urine because you feel sudden and strong urinary urgency and cannot control it?		
1. Never	3	
2. Sometimes, or often		3
10. Can you stop and start voiding in the middle of urination?		
1. Yes, I can.	1	
2. No, I cannot.		2
11. After urinating, do you have a feeling of residual urine (a feeling that there is urine left in the bladder)?		
1. No, I do not.	1	
2. Yes, I do.		1
12. Do you often feel such urinary urgency that you want to go to the toilet immediately?		
1. No, never.	3	
2. Yes, I do.		3
3. Yes, very often.		2
13. Have you ever experienced childbirth?		
1. Yes, I have.		
2. No, I have not.		1
14. How do you feel about your urine leakage?		
1. It sometimes troubles me, or it does not bother me very much.	1	
2. It troubles me very much.		1
15. How much do you weigh?		
1. I weigh <65 kg.		0
2. I weigh ≥ 65 kg.		1

Results

Seventy-eight patients were enrolled in the study. Five patients were excluded from the study because they had urge incontinence (one case) or mixed incontinence (four cases). Seventy-three patients entered the study, but six withdrew of their own will, and one withdrew because of an adverse drug reaction (hepatopathy). Ultimately, the results were analyzed in 32 cases in group A and 34 cases in group B (Figure 2). Comparison of the characteristics of the patients in the two groups showed no significant differences in age, duration of symptoms, past

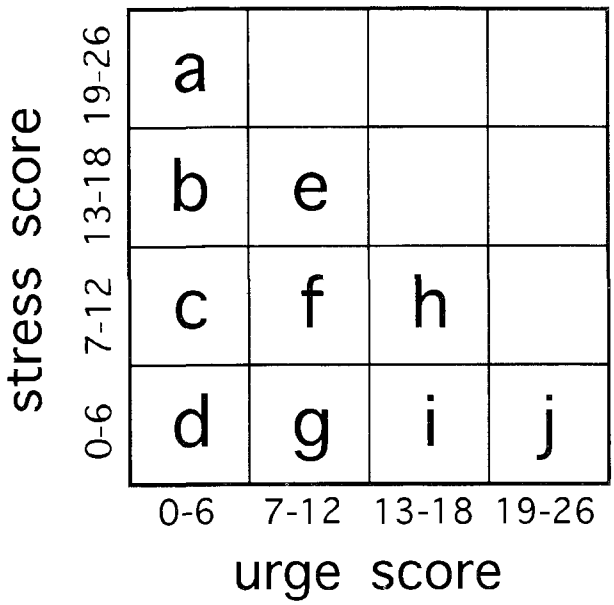

Figure 1 Diagnostic criteria of the scored UI questionnaire. Vertical and horizontal lines indicate ss (0–26) and us (0–26), respectively. Zone a refers to the zone surrounded by ss of 19–26 and us of 0–6. SI is designated zone a, b and c; urge incontinence as zones g, i and j; and mixed incontinence as zones e, f and h.

history related to UI, body mass index or severity (Table II).

In mild UI, with an ss range of 10–17, a significant decrease in ss was observed in both groups A and B at three months ($P < .0001$), and the effect was significantly higher in group A ($P < .01$) (Figure 3A). This tendency was observed for up to 18 months after the commencement of therapy. In moderate UI, with an ss range of 18–23, a significant decrease in ss was observed in both groups A and B ($P < .001$) at three months ($P < .001$), and the effect was significantly higher in group A in the first 12 months of therapy ($P < .005$) (Figure 3B). In severe UI, with an ss range of 24–26, ss decreased as therapy proceeded, but no significant difference was detected between groups A and B except at nine months of therapy (Figure 3C). As shown in Figure 3D, evaluation of all the cases as a whole revealed that the therapeutic effect was significantly higher in group A up to 12 months.

When patients whose UI score failed to decrease to zero after treatment were diagnosed as "uncured" cases, the number of uncured patients in groups A and B at the end of 24 months of therapy

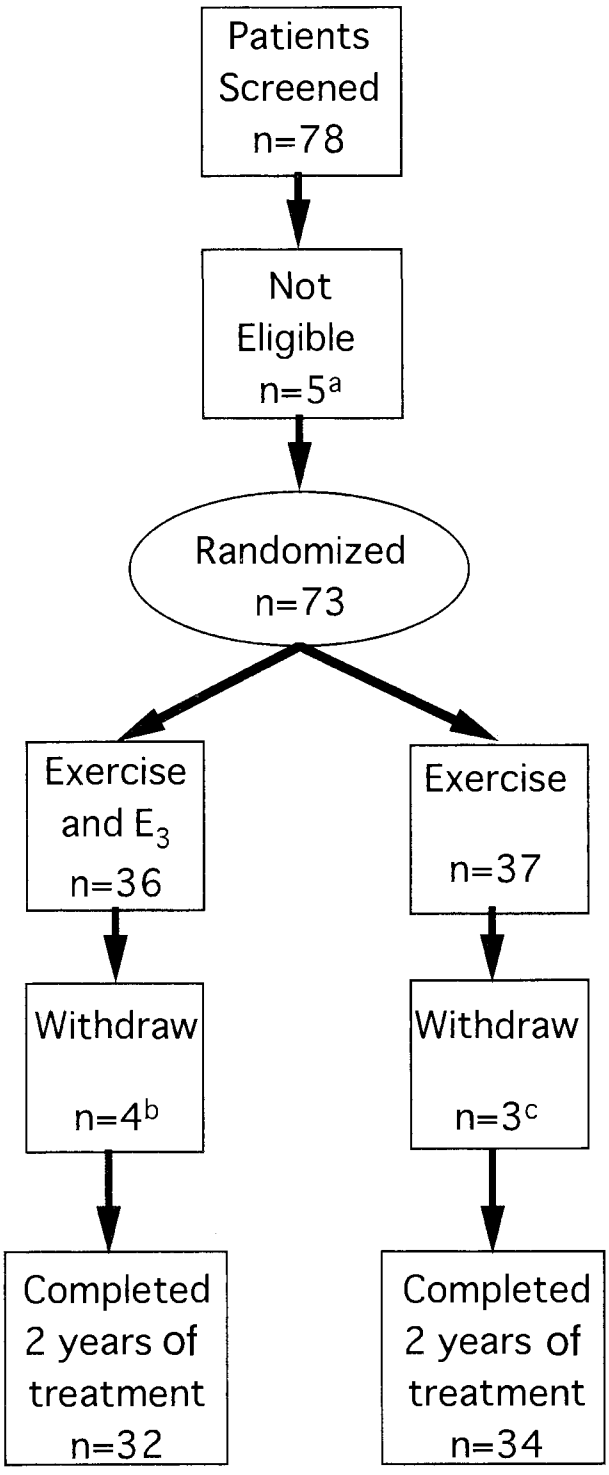

Figure 2 Patient flow diagram. Reasons for dropping out: (a) urge incontinence, 1 case, and mixed incontinence, 4 cases; (b) failure to keep clinic appointments, 3 cases, and side effects, 1 case; (c) failure to keep clinic appointments, 3 cases.

Table II *Characteristics of SI Patients*

Characteristic	Group A (n = 32)	Group B (n = 34)	*P* value
Age (yr)	58.1 ± 8.2	56.9 ± 7.5	.483
Parity	2.1 ± 1.9	2.3 ± 1.7	.755
Duration of symptoms (yr)	7.6 ± 6.1	6.8 ± 5.4	.512
Body mass index	23.9 ± 5.1	24.1 ± 4.8	.604
Previous gynecologic surgery (%)	9.4	11.8	.185
Urethrocele and/or cystocele (%)	53.1	44.1	.422
Uterine prolapse (%)	15.6	5.0	.113
UI score			
ss	19.9 ± 3.5	18.6 ± 4.1	.602
us	3.1 ± 2.2	2.9 ± 3.4	.595
Classification of severity by UI score (%) (patient no.)			.509[a]
Mild	37.5 (8)	32.4 (11)	
Moderate	43.7 (14)	52.9 (18)	
Severe	18.8 (6)	14.7 (5)	

NS by Student's *t* test ([a]χ^2 test).

was 0/12 and 2/11, respectively, in mild UI, 3/14 and 5/18 in moderate UI, and 4/6 and 4/5 in severe UI. Thus, the efficacy rates at two years in groups A and B were 78.1% and 67.6%, respectively, demonstrating significantly higher efficacy in group A ($P < .001$).

Kaplan-Meier analysis showed that the cumulative morbidity rate in mild SI patients after the start of treatment was significantly lower in group A than in group B, but no significant differences between the two groups were observed in either moderate or severe SI (Figure 4).

Discussion

While there are no objections to the significance of PFME as first-line therapy for SI,[4,8,9] because it takes a long time for PFME to exert a therapeutic effect, it is not rated as highly clinically for the treatment of UI as are anticholinergic agents.[10,11] We therefore investigated the clinical effects of PFME combined with E_3 to evaluate whether PFME is as reliable for SI as anticholinergic agents are for UI. We chose E_3 for this study because the risks of carcinogenesis and other adverse effects seem to be lower with E_3 than with other estrogens, and the effects on the urinary tract are considered to be stronger in E_3.[12,13]

The female lower urinary tract and genitalia both develop from the urogenital sinus embryologically. Although the female genitalia are obviously target organs of estrogen, it also influences the tunica mucosa of the lower urinary tract and urethra. Iosif et al[14] reported that high-affinity estrogen receptors are present in the female urethral tract and that they are identical to the receptors in the vagina. It is now thought that estrogen stimulates the smooth muscle, epithelial cells, connective tissue around the urethral tract and the blood vessel floor by binding to the receptors in the urethra and trigone of the bladder. This in turn increases the concentration of α-adrenergic receptors; that leads to enhancement of the urine-collecting function resulting from an increase in adhesion of the tunica mucosa of the urethra and elevation of maximal urethral pressure.[7,15] The results of our study demonstrate that there are significant interactions between estrogen and the female lower urinary tract because the combination of E_3 and PFME was significantly more effective even three months after the commencement of therapy than was PFME alone. The effect of E_3 persisted for as long as 18 months in the mild UI groups. The finding that the combined effect of E_3 could be detected for up to 12 months in the evaluation of all the cases as a whole is important because it indicates the need to use E_3 with PFME for at least one year in SI.

In this study, the severity of UI was classified based on the ss obtained from our original UI score questionnaire. The severity of UI is usefully classified on the basis of pad tests using the criteria defined by the ICS,[6] but it requires patients to go through prescribed motions for an hour. The pad test, however, is distressing to patients because many of them are aged. In a previous study, we reported that the relationship between the values obtained in pad tests and the ss based on UI scores can

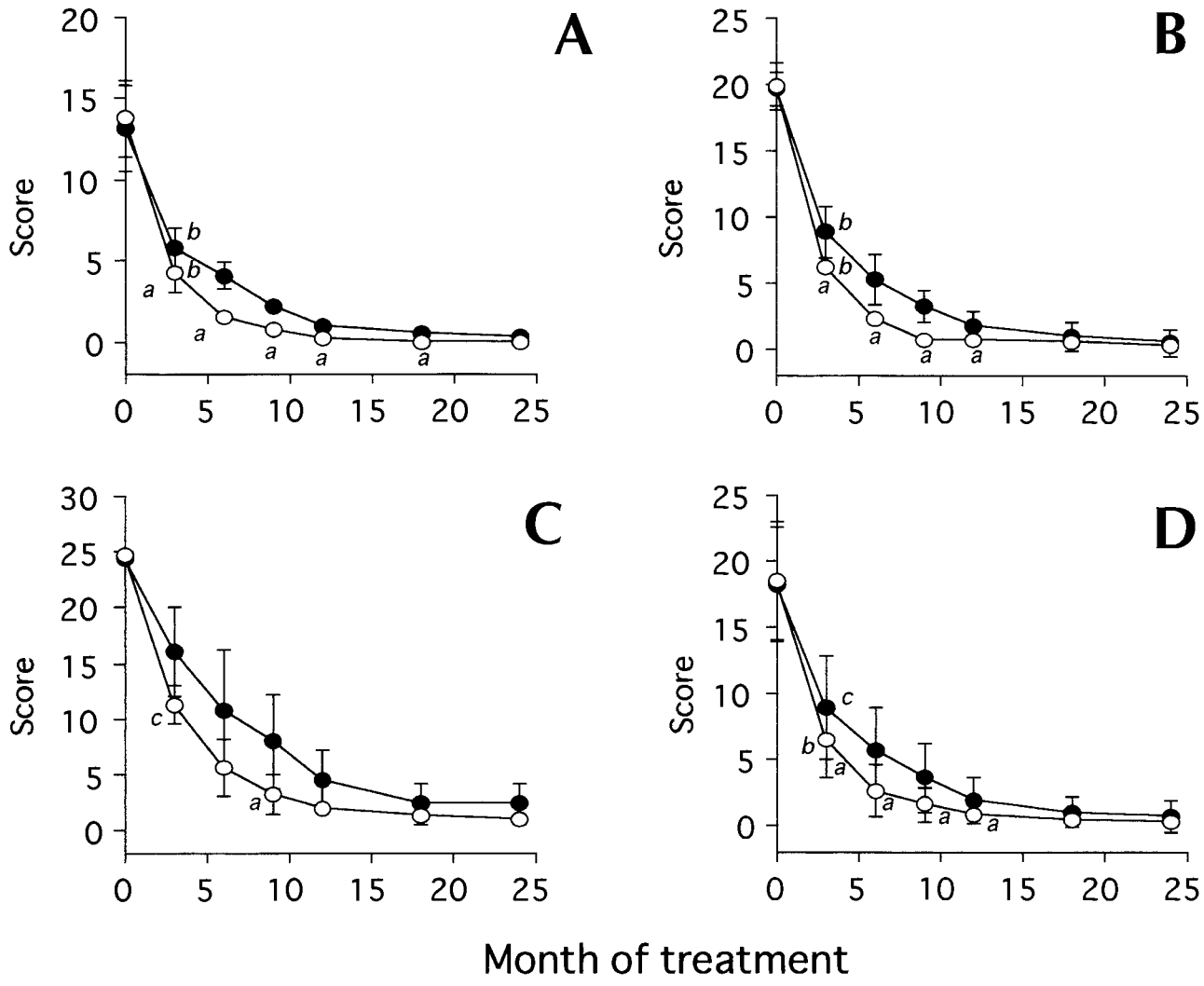

Figure 3 Changes in stress scores in the mild SI groups. (A) Open circles represent the PFME-plus-E_3 group (n = 12); closed circles represent the PFME-only group (n = 11). (B) Changes in ss in the moderate SI group. Open circles represent the PFME-plus-E_3 group (n = 14); closed circles represent the PFME-only group (n = 18). (C) Changes in ss in the severe SI groups. Open circles represent the PFME-plus-E_3 group (n = 6); closed circles represent the PFME-only group (n = 5). (D) Changes in ss in the previous cases. Open circles represent the PFME-plus-E_3 group (n = 32); closed circles represent the PFME-only group (n = 34).

be expressed as follows: Log[values from pad tests] = 0.051 × [ss based on UI scores] − 0.207 (r = .830, P < .0001). Based on the theoretical values obtained from this formula, we defined cases with ss between 10 and 17 as mild UI, those with scores between 18 and 23 as moderate UI and those with scores between 24 and 26 as severe UI, and this classification was used in the present study.[3]

There are few other reports on the therapeutic effects of PFME on SI, and the efficacy rate was around 50%.[8,9] In our study, the efficacy rate obtained with PFME alone was 67.6%, slightly higher than in other reports. We attribute the higher rate to the consultation system we employed, with patients thoroughly instructed on how to carry out PFME until they had mastered it completely. After two years of therapy, excellent clinical effects were obtained, with the final efficacy rate of the combination of E_3 and PFME as high as 78.1%. Moreover, the efficacy rate in the mild and moderate SI groups was as high as 88.5%; that indicates that E_3 was very effective in SI. Furthermore, in the mild group, E_3

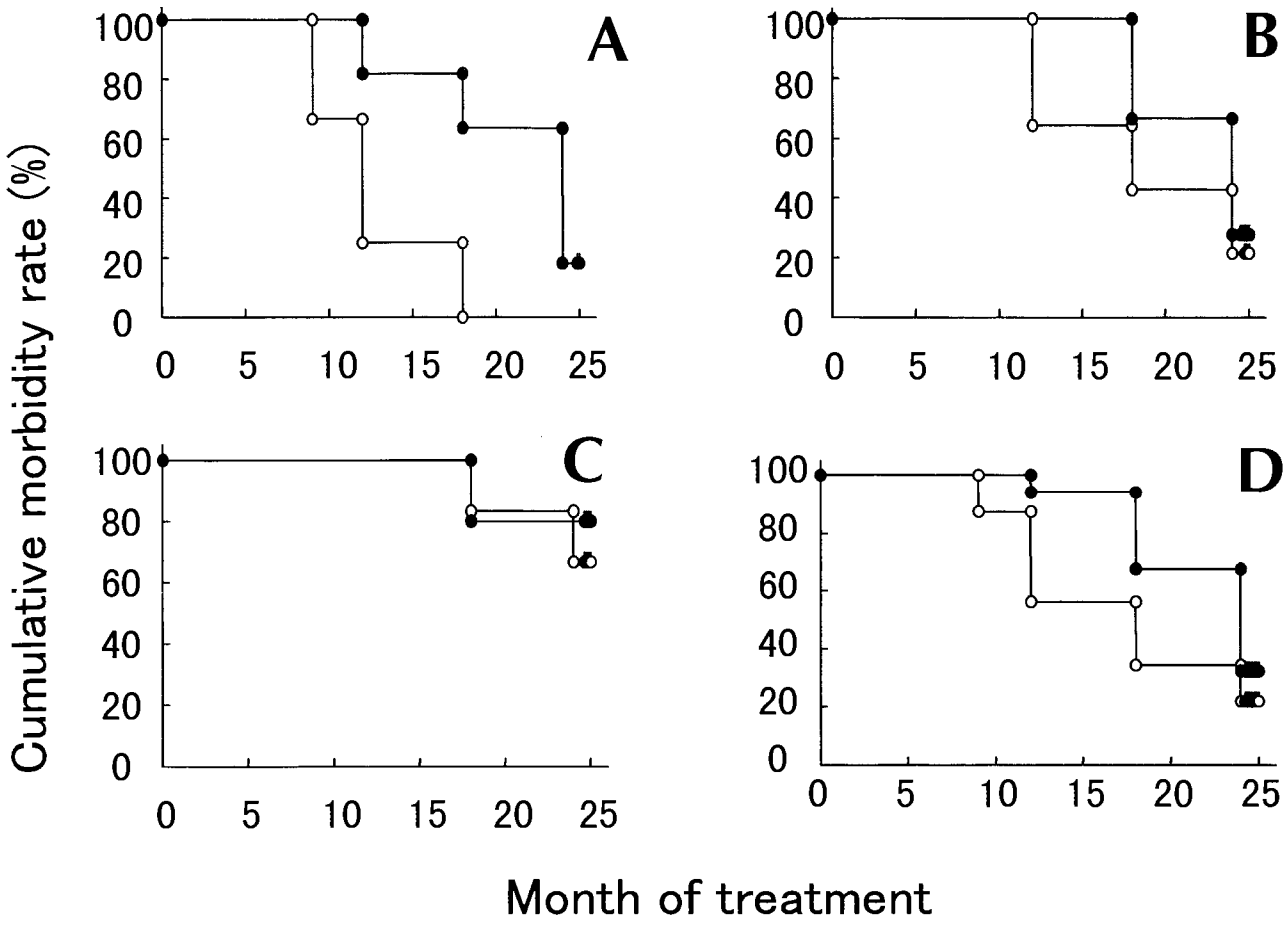

Figure 4 Kaplan-Meier analysis of the cumulative morbidity rate in SI patients after the start of treatment in (A) mild, (B) moderate, (C) severe and (D) all SI patients. Open circles represent the PFME-plus-E_3 group (n = 12, 14, 6 and 32 in A, B, C and D, respectively); closed circles represent the PFME-only group (n = 11, 18, 5 and 34 in A, B, C and D, respectively). A significant difference between the two treatment groups was observed in the mild SI patients (A) ($P < .005$).

plus PFME combination therapy significantly decreased the cumulative morbidity rate in SI patients as compared with PFME therapy (Figure 4). This result is excellent, equal to the effect of anticholinergic agents on UI, and suggests that combination therapy can be applied to cases in which surgical therapy is indicated.

Based on the above, we think that combined therapy consisting of E_3 and PFME should be first-line therapy for SI. Its clinical usefulness in SI patients is increasing in the aging global population.

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