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Changes in Hematologic Parameters during Treatment with Medroxyprogesterone Acetate for Breast Cancer

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To elucidate the etiology of the thrombogenic effects of high-dose medroxyprogesterone acetate (MPA) in the treatment of breast cancer, hematologic parameters were sequentially assessed in 12 patients receiving MPA 800 mg p.o. daily for 6 months as adjuvant hormone therapy after mastectomy. The results were as follows. (1) Coagulation system: levels of factor VII and fibrinogen decreased significantly, whereas factors II and IX increased significantly, with a shortened activated partial thromboplastin time. (2) Fibrinolytic system: plasminogen and α_2-plasmin inhibitor-plasmin complex increased, whereas fibrinogen degradation products remained low. (3) Anticoagulation system: antithrombin III increased significantly. (4) These changes were most marked after 2 or 4 weeks of MPA treatment, and returned to the pretreatment level one month after discontinuation of treatment. (5) No patients in this study developed thromboembolic disease during or after MPA administration. These results indicate that MPA may induce a hypercoagulable state, but this state does not directly lead to the development of thrombosis.

Key words: Medroxyprogesterone acetate — Thromboembolism — Breast cancer — Hematologic parameter

In recent years, high-dose MPA[3] has proved to be one of the most effective agents for the treatment of breast cancer.[1–3] However, MPA causes various adverse effects, including abscess formation, weight gain, Cushingoid syndrome, mild tremor, vaginal bleeding, muscle cramps, and thromboembolic disease,[4,5] which may develop into a life-threatening condition. Therefore, careful monitoring should be performed during therapy in order to detect the possible occurrence of this otherwise fatal complication.

Regarding the influence of progestagens on the blood coagulation systems, several studies have been performed in women receiving combined progestagen-estrogen or progestagen-only contraceptives.[6–9] However, the results obtained so far have been conflicting. Some studies demonstrated reductions of partial thromboplastin time,[6] decreased factor II,[6] and modification of thromboelastographic amplitude,[7] whereas others showed no change in the blood coagulation systems.[8,9]

The effects of high-dose MPA on the blood coagulation system have been poorly documented, except for two studies of patients with advanced breast cancer.[10,11] It is well known that tumor load alone,[12,13] or chemotherapy[14] may induce hypercoagulability, which may enhance the adverse effect of MPA. Therefore, in order to clarify the etiology of the thromboembolic effect of MPA, studies should be carried out in patients without these potentially thrombogenic factors. No reports based on this principle are available at present.

In this study we sequentially assessed hematologic parameters in breast cancer patients receiving only high-dose MPA as an adjuvant hormone therapy, in order to elucidate the role of MPA on the development of thromboembolic disease.

MATERIALS AND METHODS

Twelve breast cancer patients treated with standard radical or modified radical mastectomy (Group 1) and 5 preoperative breast cancer patients (Group 2) were entered into this study. Group 1 was composed of 7 premenopausal and 5 postmenopausal women, and Group 2 contained 1 premenopausal and 4 postmenopausal women. The ages of Group 1 and Group 2 patients were in the ranges of 37–64 years (mean: 49.1) and 39–68 years (mean: 57.6), respectively. Apart from one extremely obese patient in Group 1, all patients were within the standard weight range (45–55 kg). No patients had coagulation abnormalities, liver disorder, hyperlipidemia,

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[3] Abbreviations used are: MPA, medroxyprogesterone acetate; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrinogen degradation products; α_2PIPC, α_2-plasmin inhibitor-plasmin complex; At III, antithrombin III; FSH, follicle stimulating hormone; LH, luteinizing hormone.

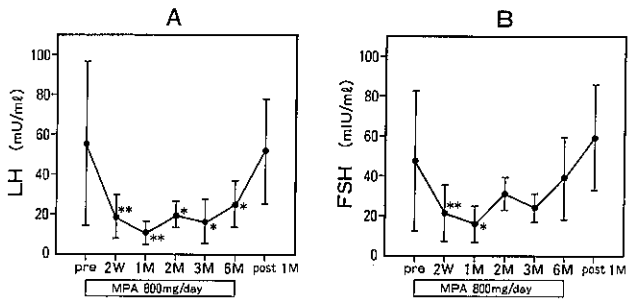

Fig. 1. Effect of oral MPA administration on mean (+SEM) serum LH (A) and FSH (B) levels in Group 1 breast cancer patients. Profiles of Group 1 patients are described in "Materials and Methods." Levels are significantly different from pretreatment levels, according to Student's t test for paired values. * $P<0.05$, ** $P<0.01$.

clinically evident cardiovascular disease, or distant metastases at the time of entry into the study.

As adjuvant hormone therapy, Group 1 patients were orally administered 800 mg of MPA per day for 6 months, starting 2 weeks after mastectomy. Group 2 patients were given 1200 mg per day for 1 week prior to surgery as a preoperative treatment.

The following parameters were measured: PT, APTT, factors II, VII, VIII, IX, X, XI, and XII, fibrinogen, FDP, plasminogen, α_2PIPC, and AT III. In addition to these parameters, FSH and LH were also measured.

In Group 1, samples for the above tests except α_2PIPC were collected immediately before treatment, and at 2 weeks, 1, 2, 3 and 6 months after the start of MPA treatment, and 1 month after the termination of treat-

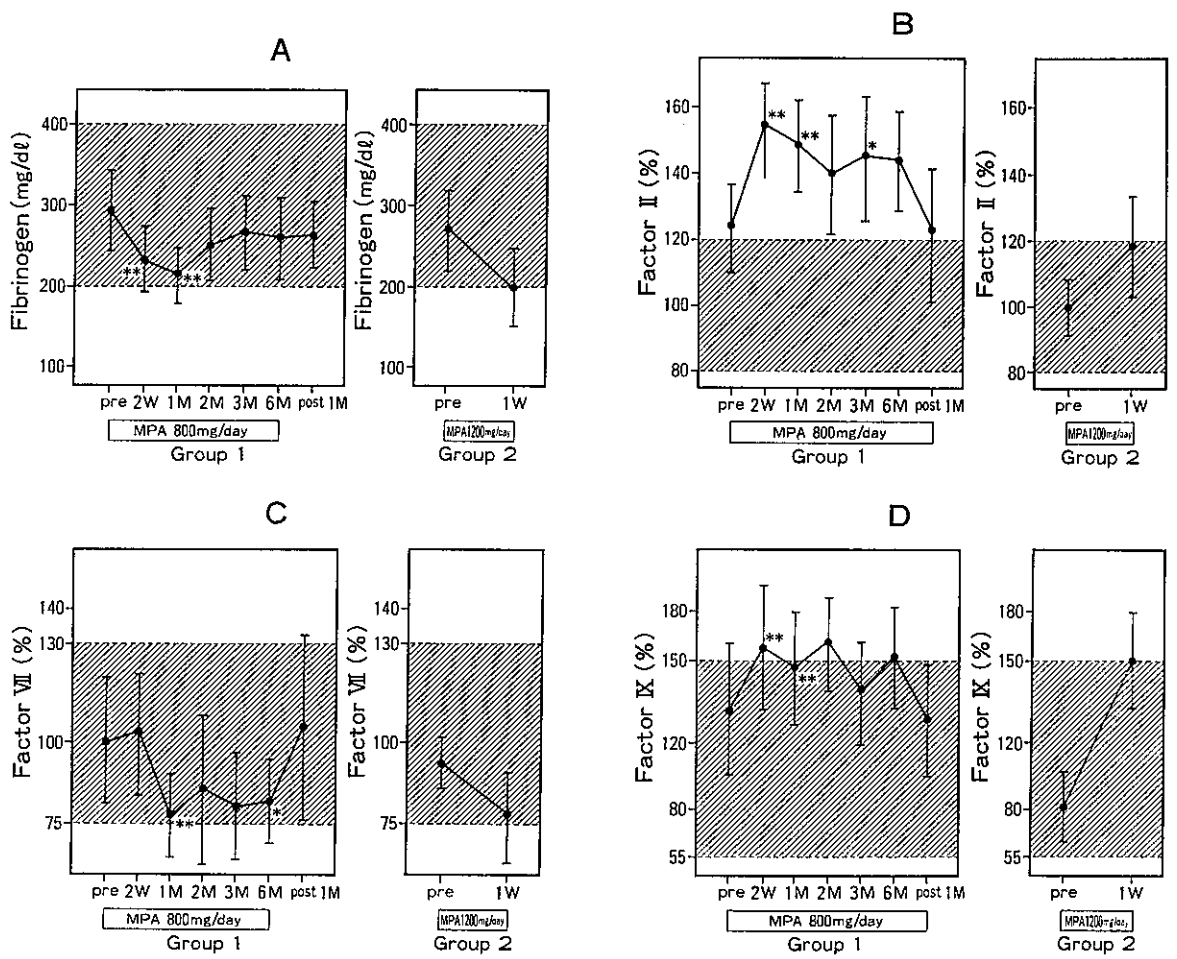

Fig. 2. Effect of oral MPA administration on mean (+SEM) serum fibrinogen (A), factor II (B), factor VII (C), and factor IX (D) levels in breast cancer patients. Profiles of Group 1 and 2 patients are described in "Materials and Methods." The hatched area represents the normal range. Levels are significantly different from pretreatment levels, according to Student's t test for paired values. * $P<0.05$, ** $P<0.01$.

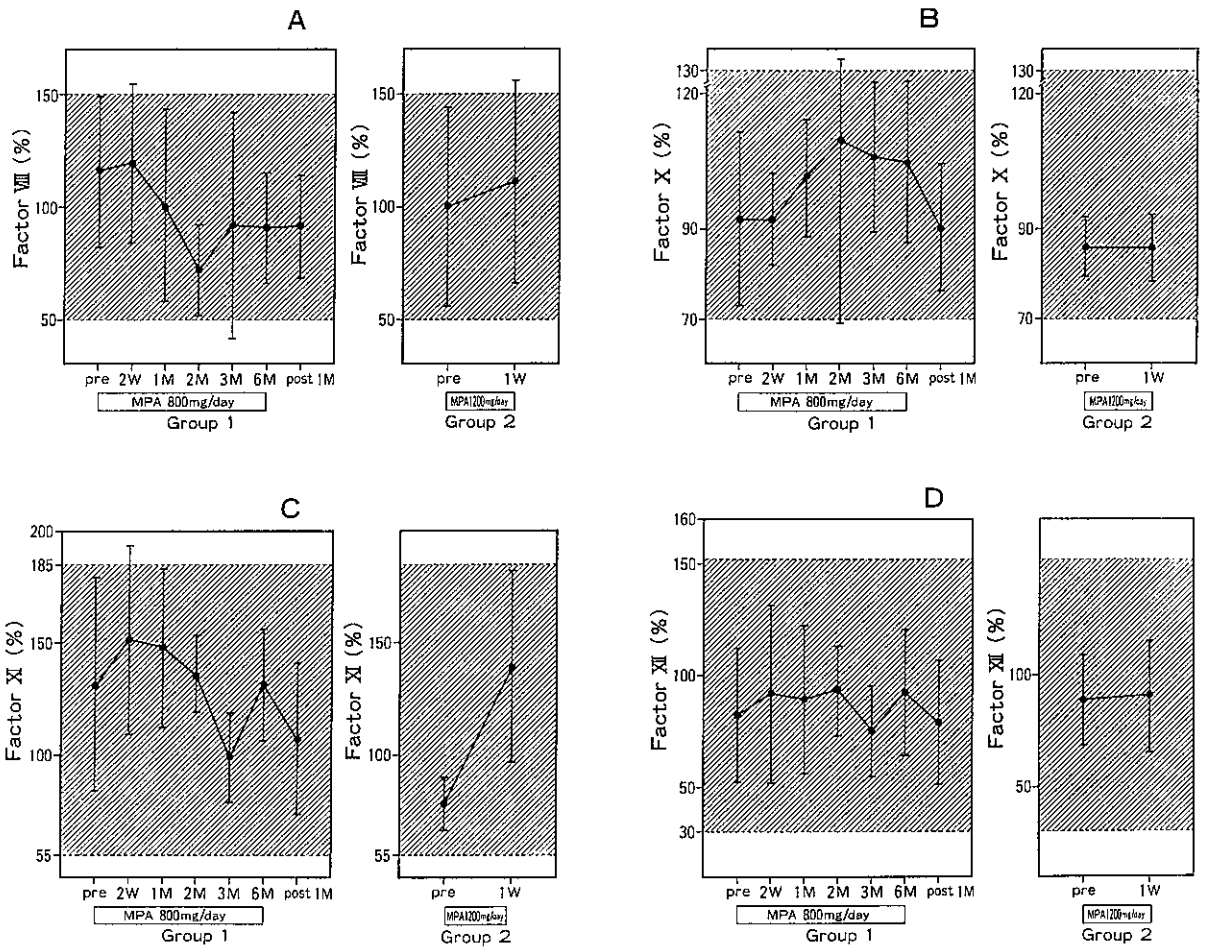

Fig. 3. Effect of oral MPA administration on mean (+SEM) serum factor VIII (A), factor X (B), factor XI (C), and factor XII (D) levels in Group 1 and 2 breast cancer patients. The hatched area represents the normal range.

ment. In Group 2 the same measurements were performed prior to treatment and 1 week after the start of medication.

Student's *t* test for paired values was used for statistical analysis.

RESULTS

Effect of MPA on serum gonadotropin levels Changes in serum LH and FSH levels are shown in Fig. 1. Both LH and FSH started to show a significant decrease as early as 2 weeks after treatment, with a trough 1 month after the start of MPA treatment. Their levels returned to the pretreatment levels after discontinuation of treatment.

Effect of MPA on the coagulation system Changes of blood coagulation factors are shown in Figs. 2 and 3. In Group 1, significant changes occurred in fibrinogen and factors II, VII, and IX during MPA treatment (Fig. 2). Fibrinogen (Fig. 2A) and factor VII (Fig. 2C) levels decreased significantly 2 weeks and 1 month after the start of MPA treatment, respectively. Similar changes were observed in Group 2, which demonstrated the early effects of MPA treatment. In contrast, in Group 1, factor II (Fig. 2B) and IX (Fig. 2D) levels increased significantly as early as 2 weeks after the start of MPA treatment, showing similar changes to those in Group 2. Factors VIII, X, XI, and XII showed no significant change throughout the treatment period (Fig. 3A–D).

APTT (Fig. 4A) was significantly shortened in Group 1 with similar changes in Group 2. However, PT (Fig. 4B) showed no significant change.

Effect of MPA on fibrinolytic and anticoagulation systems Changes of plasminogen, and α_2PIPC are shown in Fig. 5A and 5B, respectively. The level of plasminogen increased significantly during MPA treatment in Group 1 with similar changes in Group 2. The α_2PIPC, which was

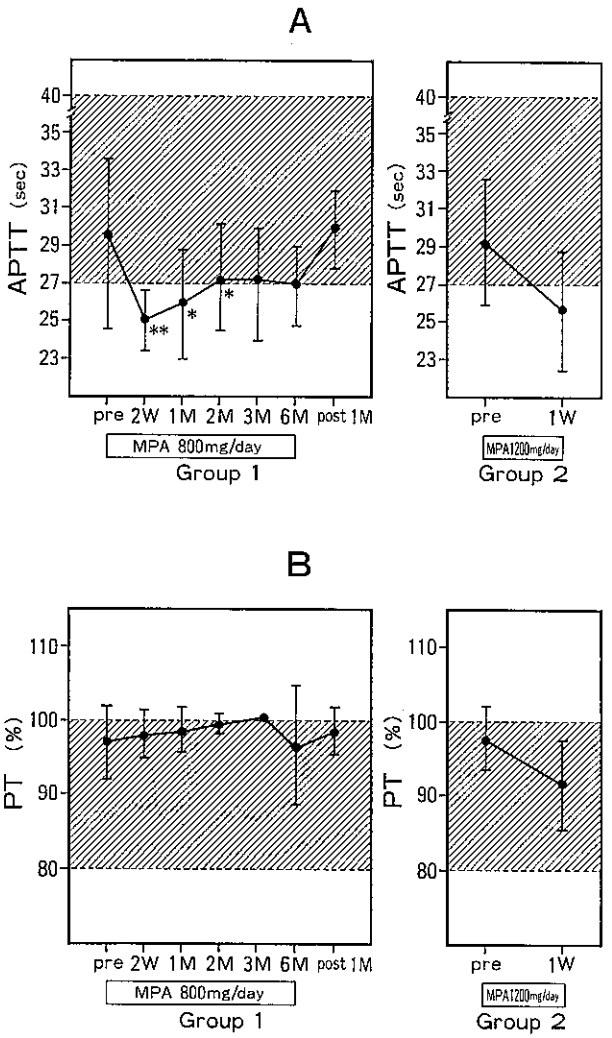

Fig. 4. Effect of oral MPA administration on mean APTT (A) and PT (B) in Group 1 and 2 breast cancer patients. The hatched area represents the normal range. Levels are significantly different from the pretreatment levels, according to Student's t test for paired values. * $P<0.05$, ** $P<0.01$.

measured only in Group 2, was increased above the normal range. In spite of the significant changes of plasminogen and α_2PIPC, FDP (Fig. 5C) was in the normal range throughout the observation period.

The level of AT III was significantly increased in Group 1 with similar changes in Group 2 (Fig. 6).

Time-course of changes in parameters The changes in hematologic parameters induced by MPA were most marked 2 or 4 weeks after the start of MPA treatment. After discontinuation of MPA treatment, the parameters returned to the pretreatment levels.

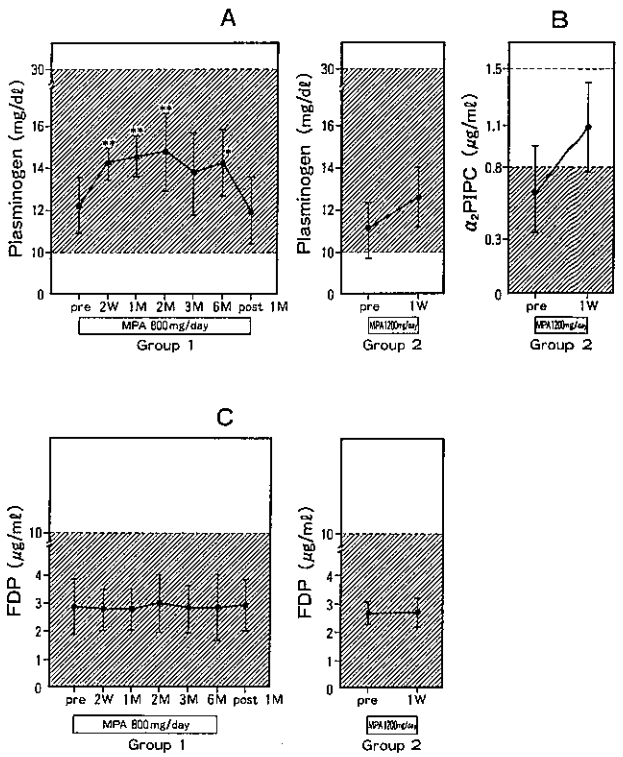

Fig. 5. Effect of oral MPA administration on mean (+SEM) serum plasminogen (A), α_2PIPC (B), and FDP (C) levels in Group 1 and 2 breast cancer patients. The hatched area represents the normal range. Levels are significantly different from pretreatment levels, according to Student' t test for paired values. * $P<0.05$, ** $P<0.01$.

No patients in this study developed thromboembolic disese during the observation period.

DISCUSSION

At our institution, the incidence of thromboembolic complication so far encountered during high-dose MPA treatment with or without chemotherapy is 2.1% of 292 breast cancer patients to date. This incidence is the same as that of Ganzina (1.8%) and Bastert (2.1%),[15,16] and is much higher than the incidence of thromboembolic disease in the general population (0.1%).[17] It has been reported that the use of combined progestagen-estrogen oral contraceptives significantly increases the risk of thromboembolism.[18] Although this adverse effect is considered to be related to the estrogen component of oral contraceptives,[8,9,19] there are some reports that low-dose progestagen contraceptives also induce changes of hematologic parameters.[6,7,20] Studies of recurrent breast cancer patients have indicated that high-dose MPA induces a state of hypercoagulability.[10,11]

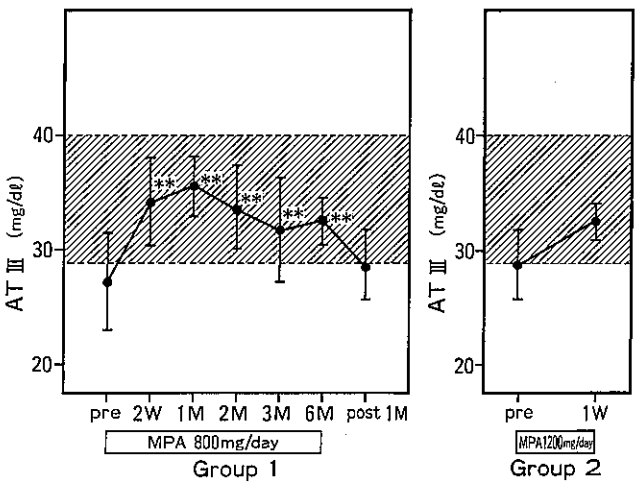

Fig. 6. Effect of oral MPA administration on serum ATIII levels in Group 1 and 2 breast cancer patients. The hatched area represents the normal range. Levels are significantly different from pretreatment levels, according to Student's t test for paired values. * $P<0.05$, ** $P<0.01$.

In this study we demonstrated increased factors II and IX and plasminogen, decreased factor VII and fibrinogen, and no change in factors VIII, X, XI and XII. These results are not consistent with the results of other studies of progestagen contraceptives, which showed no change or decreased factor II,[6, 20] no change in plasminogen,[9] no change in factor VII,[7] no change in fibrinogen,[6, 7, 9] increased factor VIII,[19] or decreased factor X.[19] These discrepancies may be due to the use of different dosages of MPA, either higher or lower.

Rosso *et al.* studied blood coagulation changes in breast cancer patients receiving high-dose MPA for metastatic lesions, and not for adjuvant therapy as in our study.[10, 11] They reported that although PT showed no significant change, PTT was shortened significantly. These results are consistent with our study. However, they found a decrease in AT III, and an increase in fibrinogen, which are totally different from our findings.

Although several discrepancies exist between our data and those of Rosso *et al.*, we believe that the changes observed in our study can be attributed to the effect of MPA itself, for the following reasons. (1) Tumor load and/or anticancer drugs have been recognized to contribute to thrombogenesis.[12–14] Therefore, our patients who received high-dose MPA for adjuvant therapy after surgery were particularly suitable subjects for the assessment of whether or not the drug itself could actually affect the coagulation systems. (2) The early changes observed during the first 2 weeks in Group 1 were similar with those of Group 2, which provides information on the initial effects of MPA treatment. (3) The parameters which showed significant changes during the treatment period recovered to the pretreatment levels after discontinuation of treatment. The profile of changes in these hematologic parameters correlates closely with changes in LH and FSH, which were previously shown to occur by feedback mechanisms during MPA treatment.[21]

It is difficult to determine whether or not these hematologic changes induced by MPA reflect a thrombotic state clinically. The observed rises in AT III and plasminogen could be interpreted as a physiologic compensatory hyperactivity of the anticoagulation and fibrinolytic systems, functioning as a homeostatic counterbalance for the hypercoagulable state. It is also possible that these changes only reflect the anabolic action of MPA.[22] Further studies are necessary to identify the underlying mechanism of these changes.

In this study, no patients developed thromboembolic disease during the observation period, and FDP was in the normal range during MPA treatment. However, most thromboembolic events seen in our patients with recurrent breast cancer receiving MPA in another study occurred approximately 1 month after starting MPA. This latent period correlates with the time when the changes of parameters seen in this study become most marked, suggesting that these changes are closely related to the occurrence of thromboembolism.

These findings indicate that MPA may induce a hypercoagulable state, but this state does not directly lead to the development of thrombosis. When other risk factors, such as hypertension, diabetes mellitus, obesity, hyperlipidemia, surgery, chemotherapy, and advanced cancer are also present, the hemostatic balance may be disrupted and thromboembolic events may occur.

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