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ORIGINAL ARTICLE

Severity scores, itch scores and plasma substance P levels in atopic dermatitis treated with standard topical therapy with oral olopatadine hydrochloride

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ABSTRACT

Atopic dermatitis (AD) is a common chronic or chronically relapsing, severely pruritic, eczematous skin disease. Recently, substance P (SP) has been demonstrated to be one of the important neuropeptides for mediating itch–scratch and stress–scratch cycles. In this study, we examined the severity scores, itch scores and plasma SP levels in 19 patients with AD treated with standard topical therapy with or without an oral antihistamine, olopatadine hydrochloride, for 4 weeks. The standard therapy decreased SCORAD scores, itch behavioral rating scores and plasma SP levels at post-treatment in the mass, but the topical therapy with olopatadine was more effective than the topical therapy alone, suggesting a potential additive effect.

Key words: atopic dermatitis, guideline, olopatadine hydrochloride, topical therapy.

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing skin disease, often associated with elevated levels of serum immunoglobulin E and a personal and/or familial history of allergy.[1] AD is a major skin disease of children that is increasing in both developed and developing countries.[2–5] Acute phases of the disease are primarily characterized by extreme pruritus (itching), which in turn leads to excoriation. Excoriation further exacerbates the underlying inflammation, setting up an "itch–scratch" cycle, resulting in chronic lesions.[6] There are a variety of known itch-associated mediators, including histamine, neuropeptides, opioids, growth factors and cytokines.[7] Among various neuropeptides, substance P (SP) has been postulated to play an important role in AD. SP promotes the production of nerve growth factor from keratinocytes and the release of histamine, leukotrienes or tumor necrosis factor from mast cells, leading to sensory nerve fiber sprouting and augmentation of skin inflammation.[8,9] Interestingly, it has also been pointed out that stress worsens dermatitis via SP-dependent neurogenic inflammation in mice.[10] Thus, SP is currently considered to be one of the key pruritogenic factors.[6,7] In keeping with this notion, abnormal expression of SP was reported in the skin lesions of AD.[11] Furthermore, it was reported that the increased plasma levels of SP significantly correlated with the disease severity in patients with AD.[12]

Standard therapy for AD is constituted of topical steroids, topical calcineurin inhibitors, emollients and oral antihistamines.[1] The standard therapy has been documented to significantly improve the severity scores and pruritus as well as quality of life in patients with AD.[13] Randomized controlled clinical trials revealed the itch-relieving effects of antihistamines in AD.[14] Olopatadine hydrochloride is a second-generation, non-sedative antihistamine that is widely used in Japan.[15,16] The antihistamine has been shown to potentially reduce the serum SP levels in AD when compared to other antihistamines.[17] In this study,

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Score	Itching During the Day
0	None
1	Mild itching, not annoying and not troublesome
2	Moderate itching, annoying and troublesome, may interfere with daily activities
3	Severe itching, very annoying, substantially interfering with daily activities
4	Very severe itching, interfering with daily activities
Score	**Itching During the Night**
0	None
1	Mild itching, not annoying or interfering with sleep
2	Moderate itching, annoying and troublesome, may interfere with sleep
3	Severe itching, very annoying, substantially interfering with sleep
4	Very severe itching, interfering with sleep

Table 1. Behavioral rating scores (BRS)

we examined the severity scores, itch scores and plasma SP levels in patients with AD treated with standard topical therapy with or without oral olopatadine hydrochloride.

METHODS

Patients and scoring systems

Nineteen patients with AD (14 men and five women; mean age, 27.3 years) were enrolled in this study. Nine patients (six men and three women; mean age, 24.1 years) were treated with topical therapy alone, and 10 patients (eight men and two women; mean age, 30.1 years) were treated with topical therapy with oral olopatadine hydrochloride daily (10 mg/day). The disease severity was scored by SCORAD.[18] The intensity of itch was measured by behavioral rating scores (behavioral rating scores [BRS]; 0–8 points in total) which was used in the previous clinical trial (Table 1).[14] The SCORAD scores ranged 30.3–100.4 (mean ± SD, 63.71 ± 23.20) in the group treated with topical therapy with olopatadine and from 19.0–68.5 (mean ± SD, 36.26 ± 17.48) in the group treated with topical therapy alone. The patients with higher SCORAD scores tended to be allocated to the group treated with topical therapy with oral olopatadine. All patients were treated for 4 weeks, and the clinical scoring as well as the blood sampling was performed at pre- and post-treatment. This study was approved by the Ethics Committee of Kyushu University.

Measurement of plasma SP level

Considering the instability of SP, peripheral blood was sampled in the presence of anti-proteinase solution (Kyowa Medex, Tokyo, Japan), and plasma SP levels were measured using an enzyme-linked immunosorbent assay method.[19] The plasma SP levels were examined in 37 healthy adult volunteers (normal controls) as well as in the 19 patients described above.

Statistical analysis

The data were analyzed using a Wilcoxon signed-rank test and multiple regression analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Efficacy of standard therapy on clinical scores of AD

The 4-week standard therapy for AD clearly and significantly reduced the disease severity in the mass as assessed by SCORAD (Fig. 1a). As this study was not randomized, patients with severe symptoms tended to be allocated to the topical therapy plus olopatadine group (Fig. 1b,c). The significant reduction of SCORAD scores was clearly observed in the group treated with topical therapy plus olopatadine (Fig. 1b). The decrease of SCORAD was very little in the group treated with topical therapy alone, however, all of the cases except one were kept in good control (Fig. 1c). The subjective itch intensity measured by BRS had a tendency to decrease after the 4-week standard therapy in total (Fig. 2a, $P = 0.075$). In the group treated with topical therapy plus olopatadine, the BRS significantly reduced at post-treatment (Fig. 2a), whereas it was not the case in the group treated with topical therapy alone (Fig. 2c).

Severe cases with higher SCORAD scores in the group treated with topical therapy with olopatadine

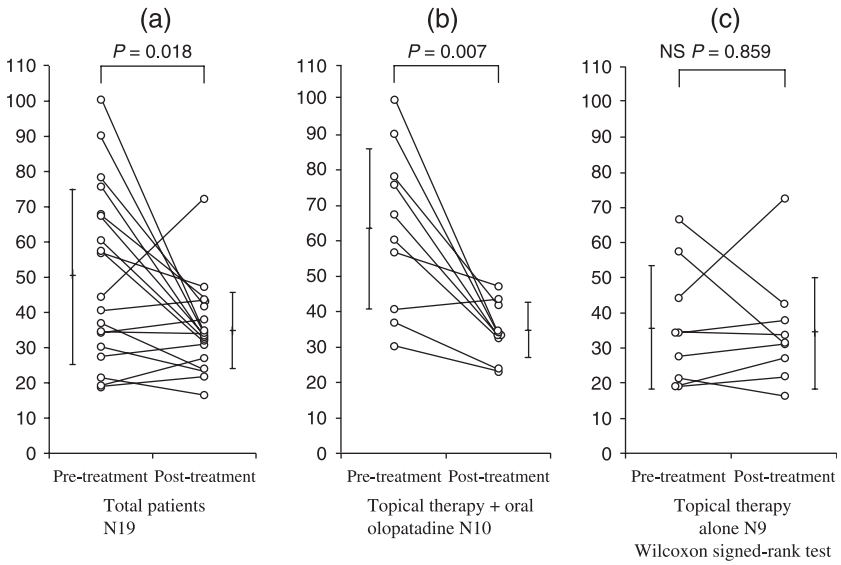

Figure 1. Pre- and post-treatment SCORAD in the patients treated with topical therapy with or without olopatadine. (a) Total patients; (b) group treated with topical therapy + olopatadine; (c) group treated with topical therapy alone.

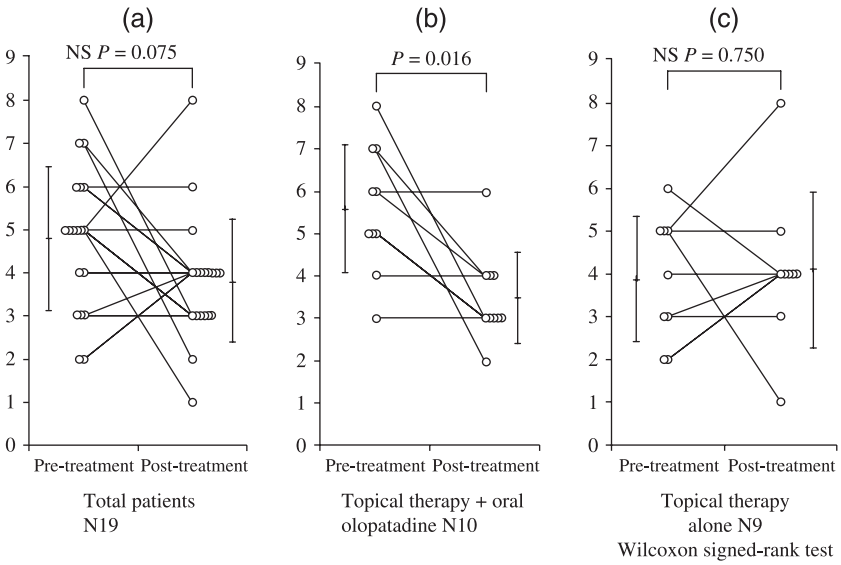

Figure 2. Pre- and post-treatment itch behavioral rating scores in the patients treated with topical therapy with or without olopatadine. (a) Total patients; (b) group treated with topical therapy + olopatadine; (c) group treated with topical therapy alone.

tended to use larger amounts of topical steroids, and the average amount of topical steroids used during the 4-week treatment tended to be larger in the topical therapy plus olopatadine group (topical steroids, 88.5 ± 88.9 g; topical tacrolimus, 15.0 ± 30.1 g) than in the topical therapy alone group (topical steroids, 42.2 ± 45.5 g; topical tacrolimus, 5.78 ± 11.2 g), although the difference was not statistically significant. However, multiple regression analysis clearly demonstrated that the dose of topical steroids contributed more to SCORAD reduction than did the administration of oral olopatadine (Table 2). In contrast, the administration of oral olopatadine contributed more to BRS-reduction than did the dose of topical steroids.

Plasma SP levels in AD

The plasma SP levels in patients with AD at pretreatment were 76.77 ± 109.89 pg/mL and were significantly higher than those of normal controls (16.46 ± 5.18 pg/mL). The plasma SP levels tended to normalize after the 4-week standard therapy in total (Fig. 3a, $P = 0.053$). The tendency for SP-normalization was observed in the group treated with topical therapy plus olopatadine (Fig. 3b), but not in the group treated with topical therapy alone (Fig. 3c).

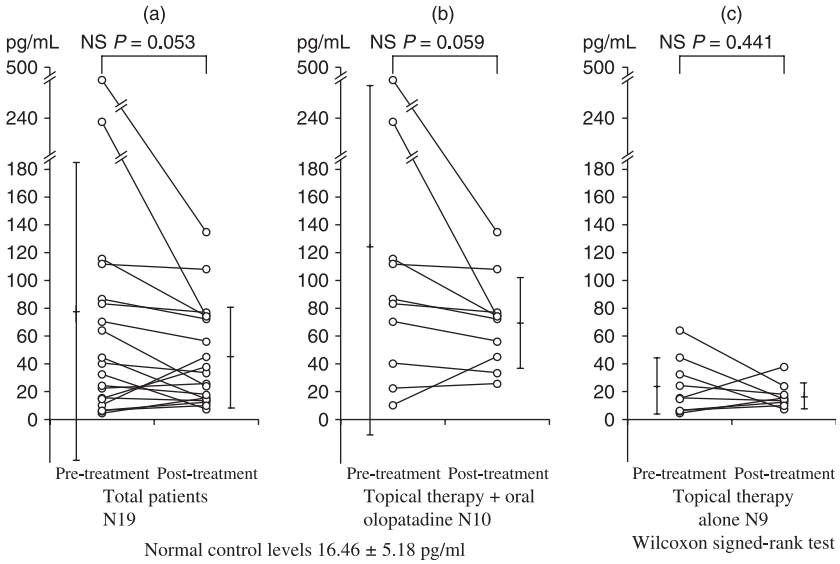

Figure 3. Pre- and post-treatment plasma substance P levels in the patients treated with topical therapy with or without olopatadine. (a) Total patients; (b) group treated with topical therapy + olopatadine; (c) group treated with topical therapy alone.

Table 2. Contribution of oral olopatadine and the dose of topical steroids to SCORAD reduction and behavioral rating score (BRS) reduction

		Oral olopatadine	Dose of topical steroids
***P*-values**	**SCORAD reduction**	0.020833	**0.002409**
	BRS reduction	**0.064572**	0.14763

DISCUSSION

In the present study, we examined the disease severity (SCORAD) and pruritus (BRS) in patients with AD at pre- and post-treatment, aiming to clarify the efficacy of standard therapy on the objective and subjective symptoms of AD.[20] Both SCORAD and BRS apparently were reduced after the standard treatment of AD. Severely affected patients with higher SCORAD scores tended to be treated with topical therapy plus oral olopatadine. Thus, it might not be surprising that the beneficial clinical effects were more evident in the group treated with topical therapy plus olopatadine than in the group treated with topical therapy alone. This may be partly due to the fact that severe cases with higher SCORAD scores in the group treated with topical therapy plus olopatadine tended to use larger amounts of topical steroids. Another possibility is that the more disrupted skin barriers in the severely affected patients may have enhanced percutaneous absorption of topical steroids, resulting in more rapid improvement than expected.[21,22] In addition, the anti-pruritic effects of olopatadine may ameliorate the itch–scratch cycle.[23] However, it is of note that the topical therapy alone could keep all of the patients except one in good control throughout the study. When the contribution of the dose of topical steroids and administration of oral olopatadine were compared, our results demonstrated that the dose of topical steroids contributed more to SCORAD reduction than to BRS reduction, and vice versa, the administration of oral olopatadine contributed more to BRS reduction than to SCORAD reduction. These data may explain the fact that the SCORAD did not correlate well with the BRS in this study (data not shown). The additive anti-pruritic effects by antihistamines have already been published in a randomized controlled study,[14] and such anti-pruritic effects would surely be beneficial to prevent excoriation in AD.

In accordance with the previous reports,[12] the circulating SP levels were elevated in patients with AD in the present study. The plasma SP levels apparently showed a tendency to decrease at post-treatment. However, the plasma SP level did not seem to be a sensitive marker for disease severity of AD ($r = 0.326$, $P = 0.173$) compared to other sensitive laboratory markers such as TARC which can range 10–40 000 pg/mL,[24,25] because the distribution window of actual values of plasma SP levels was relatively small (10 to <500 pg/mL). The declining tendency of plasma SP levels was again more evident in the group treated with topical

therapy plus olopatadine than in the group treated with topical therapy alone. Kojima *et al*. reported that the oral administration of olopatadine significantly reduced the skin concentration of SP as well as eruption scores in the murine contact hypersensitivity model induced by hapten painting.[26] Izu and Tokura examined the effects of antihistamines on the serum SP levels of patients with AD, concluding that only olopatadine, but not cetirizine, fexofenadine or epinastine, was capable of reducing the serum SP levels.[17] They also found that there was not a significant reduction of SP levels in the group treated with topical therapy alone.[17]

The present study demonstrated the efficacy of standard therapy in the treatment of AD, although the number of AD cases examined in the study was relatively small. The 4-week topical therapy with oral olopatadine was feasible to efficiently control the severe AD patients with high SCORAD scores. Amounts of topical steroids used by Japanese AD patients were small,[27,28] which may be in part attributable to the widespread fear of steroids or steroid phobia.[29] However, the fact that addition of oral olopatadine to the standard topical therapy efficiently decreased the plasma SP levels may be favorable evidence for the patients with such steroid phobia because decreased SP would slow down itch–scratch and stress–scratch cycles that precipitate the formation and aggravation of clinical symptoms in most patients with AD.[10,30]

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