INTRODUCTION

Atopic dermatitis (AD) is a common skin disease characterized by pruritic, eczematous lesions with chronic fluctuation of remissions and relapses. It is often associated with high levels of serum IgE and a personal/family history of allergic rhinitis, allergic conjunctivitis, and asthma. The underlying pathological mechanism of AD mainly involves epidermal barrier abnormalities and disrupted Th2 cell-mediated immune response due to the genetic and/or environmental factors. Along with the topical drug therapy by using moisturizers and corticosteroids, avoiding the exposure to environmental factors that trigger flare and aggravate skin lesions of AD is implemented in the clinical practice. Food, house dust mite, pollen, animal antigens, and air pollutant are known as common factors to aggravate AD. Perspiration is also associated with the exacerbation of AD in a proportion of patients, and type I hypersensitivity...
against semi-purified sweat antigen is involved in 75% of patients with AD. Thus, skin care to remove or neutralize irritants and antigens on the skin is an important treatment measure for patients with AD.

Tannic acid (TA), a natural polyphenolic and protein-denaturing agent contained in grapes and green tea, has been reported to have potent anti-inflammatory, antioxidant, antimicrobial, antimutagenic, and anticarcinogenic activities. It also has the potential of diminishing histamine-releasing activity of the semi-purified sweat antigen in a dose-dependent manner. Moreover, previous reports showed that TA removes peanut antigens from peanut butter extracts by forming insoluble complexes with the allergen and reduces mite allergens. These facts indicate the possibility that external application of TA may reduce antigenicity of AD-aggravating antigens on the skin and attenuate disrupted inflammatory responses in AD lesions, contributing to the improvement of AD symptoms. We here conducted a double-blind cross-over trial to assess the efficacy of bath additive containing TA (TA-bath additive) on pruritus in patients with AD.

2 | METHODS

This randomized, double-blind, cross-over study was carried out at Hiroshima University Hospital from July 2012 to September 2012. Efficacy of TA-bath additive on pruritus was assessed in patients with AD. The institutional review board of Hiroshima University Hospital approved the study protocol (the approval number, eki-583), and written informed consent was obtained from all participants.

2.1 | Participants

A total of 22 patients above 15 years with AD were enrolled in this study. They had mild-to-severe AD according to the Japanese guideline of the management of atopic dermatitis but in the constant disease conditions without change of treatment measures within the preceding one month. During this study, participants continued to use the treatment measures for AD which had started before this study. Since one patient dropped out due to the development of the
disease unrelated to the use of the bath additives. 21 of the 22 original patients were included for analysis.

2.2 | Trial design and treatment protocol

After consenting to participate in this study, patients were randomized into two groups. In one group, a sequence of the treatment with the TA-bath additive for two weeks followed by that with the bath additive without TA (placebo-bath additive) for two weeks was performed with 1 week washout period between each treatment arm, and vice versa in the other group (Figure 1).

2.3 | Preparation of bath additives and method for its use

Tannic acid-bath additive was in the form of powder filled in an aluminum package. It was composed of 2.0% TA, 89.0% sodium sulfate, 5.0% malic acid, 4.0% sodium glutamate, and 0.03% uranine, while placebo-bath additive contained no TA but 91.0% sodium sulfate, 5.0% malic acid, 4.0% sodium glutamate, and 0.03% uranine. Patients used one of these test bath additives once a day for two weeks in each treatment arm. One package of bath additive (40 g) was added and dissolved into hot water (150-200 L at 39-40°C) in a home bathtub followed by thoroughly stirring, achieving the final TA concentration of 0.00040%-0.00053%. Both bath additives with TA and without TA showed light green color after dissolved into hot water, so that participants could not distinguish the bath additive in use by color. Patients soaked their trunk and extremities in the hot water with bath additive for 5-10 minutes after washing their body. After coming out of the bath, they wiped off water on the skin using a towel and wore clothes.

2.4 | Assessment

The primary objective of this study was to assess the efficacy of TA-bath additive; the visual analogue scale (VAS) for pruritus (pruritus-VAS) was evaluated between pre- and postuse of the bath additives. The pruritus-VAS score was recorded for pruritus during morning, afternoon, and night. As the secondary objective, clinical score of skin lesions of AD was determined before and after the series of interventions. It was the sum of the intensity scores for five signs of “redness,” “papules,” “lichenification,” “desquamation,” and “exudation.” The intensity score of each of the five signs was graded on a scale of “none, 0; slight, 1; mild, 2; moderate, 3; severe, 4.”

2.5 | Statistical analysis

The statistical analysis was performed by GraphPad Prism (GraphPad Software, ver. 8.2). A P value of <.05 was considered significant.

| TABLE 1 Patients’ demographics |
|--------------------------------|
| **Total number** | 21 |
| **Gender** | M:F = 7:14 |
| **Age (median)** | 37.0 y-old (range, 17-48) |
| **Disease severity** |  |
| Mild | 3 patients |
| Moderate | 9 patients |
| Severe | 9 patients |
| **Pruritus-VAS score at the beginning of interventions** |  |
| Morning (mean ± SD) | TA arm | Placebo arm |
| Mild-to-moderate AD | 4.85 ± 2.79 | -ns- |
| Severe AD | 5.05 ± 2.60 |

Note: Data were analyzed by the Mann-Whitney test. Abbreviations: AD, atopic dermatitis; SD, standard deviation; TA, tannic acid; VAS, visual analogue scale.

3 | RESULTS

Patients’ demographics are shown in Table 1. There were no significant differences of pruritus-VAS score at the beginning of interventions between the mild-to-moderate AD and the severe AD, and between TA arm and placebo arm. The overall patient cohort demonstrated no significant decrease from baseline in any pruritus-VAS scores on the TA-bath additive, compared to placebo (Figure 2A). In the analysis stratified by AD severity, patients with mild-to-moderate disease showed a significant reduction of the VAS score of itch at night by the TA-bath additive treatment compared to placebo (Figure 2B). No significant differences in change of the itch score were found in the other periods of day. In patients with severe AD, there were no differences observed between the active and placebo-treatments in all periods of day (Figure 2B). Comparing the VAS scores before and after the intervention, the VAS scores tended to decrease during all periods of the morning, afternoon, and night in both of the TA- and placebo-bath additive arms (Figure 3A). Significant improvement of pruritus was shown in itch in the afternoon by using the TA-bath additive and in the afternoon by using the placebo-bath additive (Figure 3A). Regarding skin lesions of AD, 15 patients showed improvement with the clinical score over the series of the active and placebo interventions, while AD
Lesions were stable in five patients and worsened in one patient, resulting in the significant reduction of the clinical symptom score (Figure 3B). No adverse effects related to the use of TA- and placebo-bath additives were observed.

4 | DISCUSSION

Bathing helps patients with AD by hydrating the skin and removing scales, crusts, irritants, and antigens, but there have been only few reports on the usefulness of bath additives for AD. In this study, pruritus tended to be improved in all observed periods of morning, afternoon, and night by using either the TA- or placebo-bath additive in patients with AD. The superiority of the TA-bath additive to the placebo-bath additive was not demonstrated in the overall patient cohort. This may be because the basic ingredients of bath additive or bathing itself reduced pruritus to some extent. However, given the analysis limited to patients with mild-to-moderate AD, the efficiency of TA in the bath additive was significant on pruritus at night compared with placebo. This appears to be due to a relatively large reduction of the VAS score by the TA-bath additive and less improvement of pruritus by the placebo-bath additive than in the other cohorts. A possible explanation of such difference is that the added TA may exert its effect more effectively on mildly to moderately damaged skin than on severely damaged skin, but the effect of other ingredients in both bath additives is larger on severe AD than on mild-to-moderate AD. Moreover, bathing by using series of the bath additives with and without TA finally achieved substantial improvement of AD skin lesions. In previous reports, De Paepe et al demonstrated that rice starch as a bath additive gave a beneficial effect on chemically damaged skin.
barrier and improved skin barrier function by the formation of protective layer in patients with AD. Although Loden et al reported the skin irritation of certain bath additives and the presence of barrier-impairing residues on the skin, no adverse events including contact dermatitis occurred with bath additives taken in this study.

A clinical trial using external application of TA were studied by Shindo et al, in which the effect of aerosol spray containing 0.05% TA (TA-spray) was evaluated on pruritus in the morning, afternoon, and night in a randomized, placebo-controlled, double-blind study for adolescents and adults with AD. As a result, the TA-spray treatment significantly improved pruritus in the morning and night compared to placebo. The lower concentration of TA (0.00040%-0.00053%) in the bath additive than that in the TA-spray (0.05%) may explain no superiority of the TA-bath additive to the placebo in the overall patient cohort in this study. Moreover, the difference in effect between the TA-bath additive and the TA-spray may depend on the frequency of use. The bath additives were basically used once a day when bathing, whereas spray formulation was used on-demand multiple times a day by carrying it. Furthermore, pruritus in the afternoon was reduced by bathing with placebo-bath additive, suggesting the effect of the basic ingredients of bath additives or bathing itself on pruritus of AD. Nevertheless, this study showed...
the reduction of pruritus in the afternoon and night by using the TA-bath additive, while only in the afternoon by the placebo. It may be an advantage of bath additive to be applied over the body surface evenly after removing contamination on the skin, in comparison with the local use of the spray.

Possible mechanisms of action of TA on the AD skin have been analyzed using in vitro or in vivo animal models. In addition to the reduction of antigen activity mentioned in the introduction section,5–7 Nakamura et al12 reported that external application of TA suppressed IL-1α production in a contact dermatitis model and that TA suppresses substance permeation by forming a barrier against foreign substances such as chemicals and artificial sweat. Karuppagounder et al4 also showed that the oral administration of TA suppressed activation of NFκB signaling pathway and subsequent cytokine production in house dust mite extract-induced AD-like lesions in NC/Nga mice and contributed to the improvement of skin symptoms. Moreover, Jung et al found that the external application of TA and quercetin contributed to the reduction of skin symptoms in house dust mite extract-induced AD-like lesions in NC/Nga mice due to the suppression of Th2 cytokine expression and angiogenesis.13 All these mechanisms may have contributed to reducing pruritus of the AD skin especially that in mild-to-moderate conditions.

In the treatment of AD, pruritus ought to be properly managed; otherwise, pruritus-related scratching induces aggravations of dermatitis and may lead to contagious impetigo especially in summer. Therefore, the bath additive containing TA may be taken as a potential skin care product to manage AD skin in the mild condition.

ETHICAL APPROVAL
Research protocol was approved by Hiroshima University Hospital (the approval number, eki-583).

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CONFLICT OF INTEREST
SS and HK were employees of Bathclin Co.

INFORMED CONSENT
Informed Consent (especially for case): Yes.
Registry and the Registration no. of the Study/trial: N/A.

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