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RESEARCH ARTICLE

The effect of balneotherapy with natural mineral dissolved water on dry skin in atopic dermatitis: A phase IIa, nonrandomized, controlled study

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Abstract

Objectives: It has been known that the use of moisturizers is useful in preventing the onset and maintaining remission of atopic dermatitis (AD). We recently focused on the moisturizing effect of natural mineral dissolved water and have conducted various studies. In this study, we investigated whether the bath treatment using natural mineral dissolved water can improve dry skin in AD patient in prospective nonblind, nonrandomized controlled study.

Methods: Thirteen adults with almost clear to moderate AD took bath therapy using tap water for 13 days, followed by bath therapy using natural mineral dissolved water for 13 days. Changes in the severity scoring, patient-oriented eczema measure, pruritus numerical rating scale, transepidermal water loss (TEWL) and hydration were evaluated at day1, 14 and 28.

Results: Tap water using bath treatment did not change the severity scoring and itch associated score, and it partially decrease TEWL when compared with baseline condition. Bath treatment using natural mineral dissolved water slightly decrease eczema area and severity index (EASI) score and significantly decrease TEWL with respect to baseline condition. Moreover, in relatively severe AD analysis, bath treatment with mineral dissolved water significantly decreased EASI and TEWL.

Conclusions: Based on these results, bathing with natural mineral dissolved water may be effective in improving the dry skin of atopic dermatitis. Further studies are needed to evaluate its effects more clearly.

KEYWORDS
atopic dermatitis, barrier dysfunction, bathing, dry skin, natural mineral water

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronically relapsing allergic inflammatory skin with an increasing prevalence in the world.[1] The pathogenesis of atopic dermatitis is based on epidermal barrier dysfunction and activation of type 2 helper T (Th2) lymphocytes producing cytokine, resulting in skin inflammation and pruritus.[2–4] It has been well known that disease severity is closely related to poorer quality of life in adult AD,[5] suggesting that it is very important to control the disease activity for their daily life. It has been revealed that the use of topical moisturizers improves the moisture content of the stratum corneum, that reduced in atopic dermatitis, and restores and maintains the skin barrier function, leading to the prevention of allergen penetration, prevention of dermatitis flare-ups, and suppression of itching.[6,7] In the Japanese guidelines for atopic dermatitis 2020, the use of topical moisturizers all over the body including the sites that appear to be normal is highly recommended.[8] It is reported that mutations in filaggrin (*FLG*), a key structure of the epidermal differentiation complex which regulates homeostasis of the skin, causes various skin diseases such as ichthyosis vulgaris, AD or irritative contact dermatitis.[9] Moreover, the increased transepidermal water loss which mirrored barrier dysfunction was found in children with mutants in *FLG* before development of AD.[10,11] Interestingly, a randomized controlled trial study demonstrated that daily application of moisturizer during the first 32 weeks of life reduces the risk of AD/eczema in infants.[12] These results indicate the significance to improve the barrier dysfunction of the skin by using moisturizers in AD. However, Christie *et al*[13] demonstrated the difficulty of maintaining daily topical treatment by monitoring psoriasis patients. This fact led us to believe that moisturizing treatment as an alternative to topical therapy may reduce the burden on AD patients, resulting in maintenance of AD remission and improvement of quality of life.

We have recently noticed that laborers who handle natural mineral dissolved water, which used as a neutralizer for river acidification, felt improvement of their dry hands. Based on this fact, we hypothesized that natural mineral dissolved water might have a high moisturizing effect, and that topical application of natural mineral water may improve dry skin in atopic dermatitis, however, it is still unclear. The aim of this study is to investigate the effect of natural mineral dissolved water in restoration of dry skin in AD.

2 | METHOD

2.1 | Study design

This investigator-initiated clinical trial was designed as a prospective, nonblind, nonrandomized controlled study comparing natural mineral dissolved water with tap water (trial registration: UMIN Clinical Trials Registry, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000045876)(UMIN000040220) at a single center in Japan (Gunma University), from December 2020 through March 2021. This study was approved by the Institutional Review Board (IRB) of the Gunma University in August 2020 (IRB2020-018), and all patients were provided written informed consent and ethics committees approved the protocol. This study was performed at the Department of Dermatology, Gunma University in Japan. Treatment was started at day 1 (base line) and reviewed at day 14 and 28. Participants received daily bathing treatments at home, using tap water for thirteen days (day1–13), followed by bath salts for thirteen days (day14–27). The primary end points were score on the eczema area and severity index (EASI) and pruritus numerical rating scale (NRS).[14,15] Secondary end points were transepidermal water loss (TEWL) and hydration of forearm which were measured with DermaLab® (Cortex Technologies, Denmark) which allows collection of reproducible data.[16] The treatment for atopic dermatitis, including topical steroid ointment, moisturizer, and antihistamine medicine was continued and not changed during the study period. No topical application was done on the forearm 12 hours prior to the measurement of TEWL and hydration. The use of bathwater additive was prohibited during the study period. Adverse events were reviewed at each visit.

2.2 | Patients

Inclusion criteria were patients aged 20–65 years diagnosed with AD according to the Hanifin and Rajka criteria,[17] and the severity was almost clear to moderate (IGA<2, EASI<16).[14] Exclusion criteria were the following patient (1) who could not take a bath during the clinical trial period, (2) who have erosion or severe dermatitis (EASI>16), and (3) who were assessed as inappropriate for any other reason by the clinical investigator or clinical trial physician. A total of 13 Japanese patients (8 males, 5 females; mean ages ± standard error (SD), 25.9 ± 5.2 years) were selected (Table 1). All patients had been diagnosed as atopic dermatitis in their childhood, and they had been receiving treatment of AD for one month prior to the start of this study.

2.3 | Treatment and evaluation protocol

All participants took baths (day1–13: 200 L tap water, 38–42°C, 5 minutes, day 14–27: Sangolite BATH SALT® 100 g dissolved in 200 L tap water) at home every day. The Sangolite BATH SALT® was made and provided by GUDi CO., Ltd, and its ingredients are shown (Table 2). The pH values of the bath water after dissolving the Sangolite BATH SALT® was designed to be mild acidic with a pH of 4–5, which is considered optimal for skin care.[18] The changes in the severity of dermatitis were assessed using static investigator's global assessment (sIGA)[19] and modified EASI score,[14,20] pruritus numerical rating scale (NRS)[21] and patient-oriented eczema measure (POEM)[22]. Participants rest in the room (temperature 20–22°C,

TABLE 1 Patient demographics and baseline disease characteristics

Characteristic	Total patients ($n = 13$)
Age, years,	
Mean (SD)	25.9 (5.2)
Range	21–38
Gender	
Male	8 (61.5%)
Female	5 (38.5%)
EASI total score	
Mean (SD)	4.5 (2.2)
Range	0.4–7.8
IGA	
Mean (SD)	1.7 (0.5)
Range	1–2
BSA, %	
Mean (SD)	15.5 (8.0)
Range	3–30
NRS	
Mean (SD)	4.5 (2.1)
Range	2–8
POEM	
Mean (SD)	10.4 (3.7)
Range	3–15
TEWL, $g/m^2/h$	
Mean (SD)	14.9 (8.0)
Range	4.4–29.6
Hydration, μ Siemens	
Mean (SD)	93.5 (26.9)
Range	54.6–131.8

TABLE 2 Composition of Sangolite BATH SALT®

Contents	Sangolite BATH SALT® (wt%)	Dolomite (wt%)
Citric acid anhydride	60	
Calcium	9.2	23.1
Magnesium	4.9	12.2
Silicon	0.3	0.7
Aluminum	0.2	0.6
Potassium	0.1	0.3
Carbonated acid	25.2	63.1

humidity 40–60%) for 15 minutes before the physiological examination. TEWL and Hydration were measured at three locations on both forearms and the average value was calculated. The total score at baseline was set as 100% and the relative scores at each visit were quantified.

2.4 | Statistical analysis

Data were analyzed using GraphPad Prism 9 (version 1.0). *p*-values were calculated using the one-way analysis of variance (ANOVA), followed by Bonferroni's multiple comparisons test. $p < .05$ was considered statistically significant. Error bars represent standard errors of the mean.

3 | RESULTS

3.1 | Demographic and clinical features of AD participants

A total thirteen patients with AD patients participated in the study. Baseline demographic and disease characteristics were described (Table 1). All of the participants were Japanese, and most patients were male (61.5%) with mean age 25.9 (range 21–38). One patient (7%) was classified as almost clear (EASI<1), eleven (86%) were classified as mild (EASI<7) and one[7] was moderate (EASI<21). As for sIGA score, four participants scored 1 (almost clear) (31%) and nine scored 2 (mild disease) (69%). Overall mean of EASI total score was 4.5, mean sIGA score was 1.7, mean BSA was 15.5, mean NRS was 4.5, mean POEM was 10.4, mean TEWL was 14.9 and mean Hydration was 93.5.

3.2 | Efficacy and safety

For the primary end point analysis at day 14, each of mean value was 1.61 in sIGA (−4.5%: the least-squares mean percent change from baseline) ($p > .99$), 5.18% in EASI (−7.3%) ($p > .99$), and 4.38 in NRS (−1.7%) ($p > .99$), respectively. With respect to secondary end point, each of mean value was 11.7 in TEWL (−21%) ($p = .63$) and 99.9 in hydration (+6.9%) ($p > .99$). For the primary end point analysis at day 28, each of mean value was 1.61 in sIGA (−4.5%) ($p > .99$), 3.13 in EASI (−30.8%) ($p = .18$), and in 4.53 NRS (−1.7%) ($p > .99$), respectively. With respect to secondary end point, each of mean value was 7.23 in TEWL (−51.3%) ($p = .01$) and 90.7 in hydration (−2.9%) ($p > .99$) (Figure 1). For further study, we analyzed participants with relatively high severity of AD (EASI >4, TEWL >10). For the primary end point analysis at day 14, each of mean value was 1.75 in sIGA (−6.7%) ($p > .99$), 5.18 in EASI (−11.5%) ($p > .99$), and 4 in NRS (0%) ($p > .99$), respectively. With respect to secondary end point, each of mean value was 13.6 in TEWL (−28%) ($p = .63$) and 97.9 in hydration (+16.2%) ($p > .99$). For the primary end point analysis at day 28, each of mean value was 1.75 in sIGA (−6.7%) ($p > .99$), 3.56 in EASI (−39.2%) ($p = .005$), and 3.85 in NRS (−3.1%) ($p > .99$), respectively. With respect to secondary end point, each of mean value was 7.65 in TEWL (−59.3%) ($p = .001$) and 87.4 in hydration (+3.7%) ($p > .99$). There were no adverse effects during this study (Figure 2).

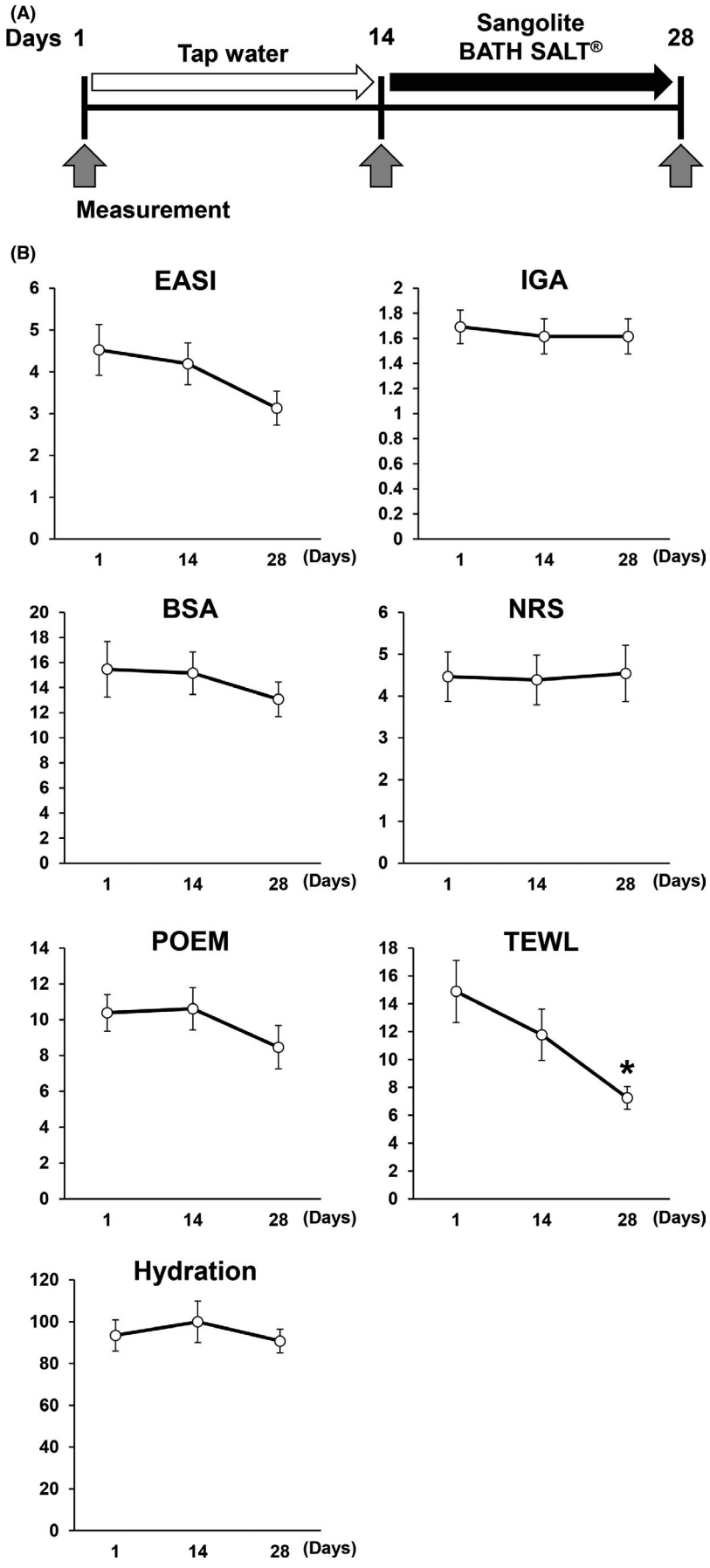

FIGURE 1 The effect of bath treatment with tap water natural mineral dissolved water on disease severity (sIGA, EASI, BSA), NRS, POEM and TEWL, hydration in AD. (A) Scheme of the experimental procedure. Physical examination was performed on day 1, 14 and 28. (B) Each panel showed the quantification of sIGA, EASI, BSA, NRS, POEM, TEWL, and hydration during experiment in all AD. $n = 13$. All values represent mean ± SEM. $^*p < .05$.

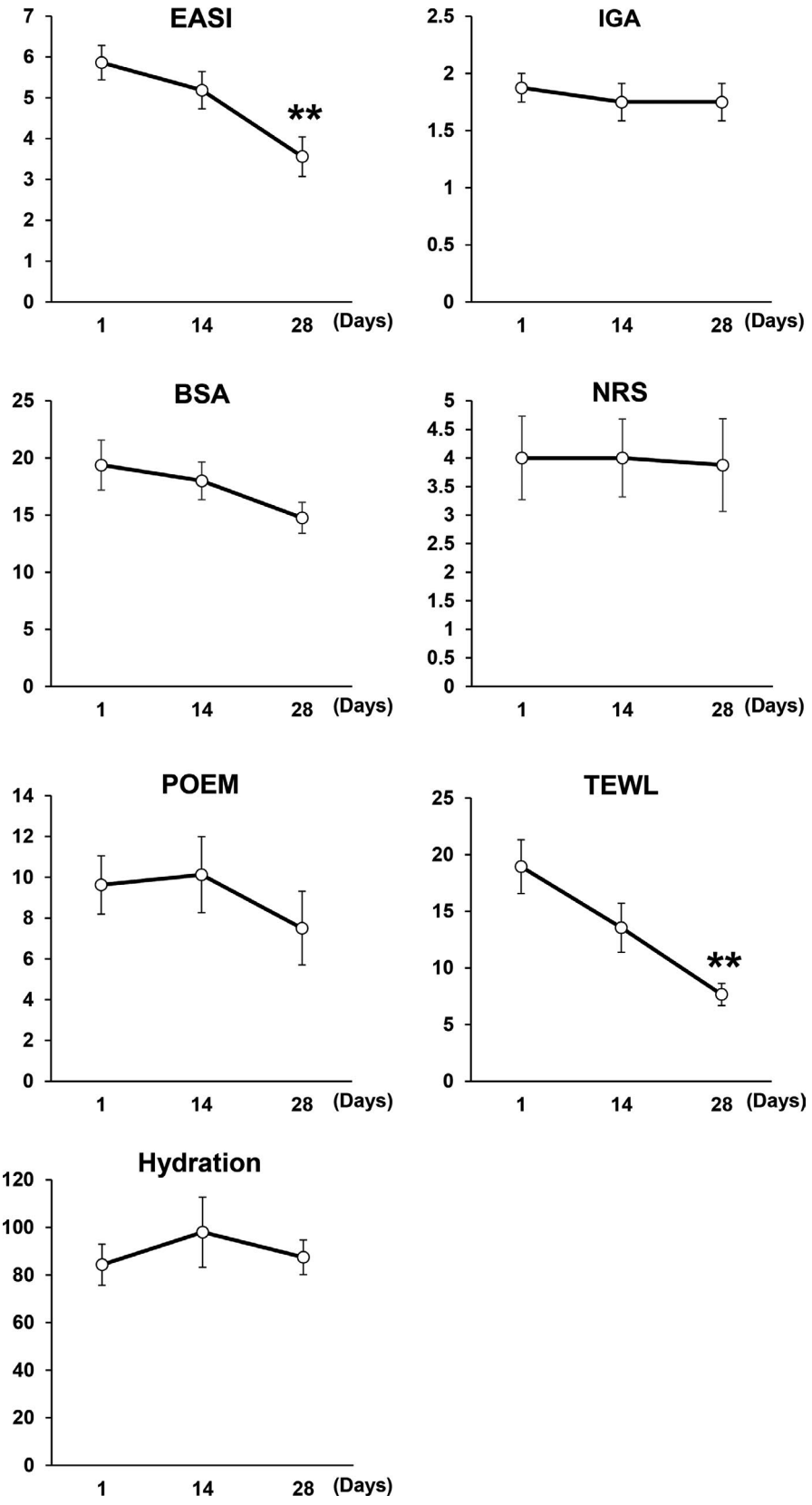

FIGURE 2 Each panel showed the quantification of sIGA, EASI, BSA, NRS, POEM, TEWL, and hydration during experiment in relatively severe AD (EASI>4, TEWL 10). $n = 8$. All values represent mean ± SEM. $^{**}p < .01$.

4 | DISCUSSION

In a prospective nonblind, nonrandomized controlled study, we investigated the effect of mineral dissolved water on the severity of adult AD patients. There are several reports which demonstrated the beneficial effect of balneotherapy on AD in human and mice.[23,24] In our best knowledge, this is the first study which revealed the efficiency of balneotherapy using natural mineral dissolved water in AD patients.

It has been demonstrated that the elevated pH caused by barrier abnormality increases kallikrein activity, resulted in the upregulation of thymic stromal lymphopoietin (TSLP) followed by Th2-type immune responses.[25] Weakly acidic (pH 4.5) moisturizers have been reported to significantly improve TEWL and itch score compared to standard moisturizers.[26] There is a possibility that the weakly acidic pH (pH 4–5) in natural mineral dissolved water might be the key factor which contributed to the improvement of dermatitis and barrier function. Another mechanistic evidence suggested that body exposure to mineral water at the spa would beneficially affect the immune system and antioxidant mechanism.[27,28] Interestingly, most of subjects took showers but did not take baths. Actually, bath treatment using tap water (day1-day13) showed partially decreased EASI score and TEWL. This result might indicate that daily bathing may contribute to the improvement of barrier dysfunction. Since we did not conduct a crossover study at this moment, we could not exclude the effect of prolonged bath treatment itself. Moreover, the current study did not set the group with only using tap water as a control to the group with only using natural mineral dissolved water. These points are major issues in this study, and they must be accurately assessed in further examination.

Dolomite is an anhydrous carbonate mineral composed of calcium magnesium carbonate. It has long been used as a source of calcium and magnesium supplements. The ratio of calcium to magnesium in dolomite (2:1) is believed to be optimal for mineral absorption.[29] After dissolving the Sangolite BATH SALT®, the calcium concentration will be about 1.14 mM and the magnesium concentration will be about 1 mM. This range of high calcium concentration is usually used for differentiation assay in human epithelial keratinocyte *in vitro*.[30] Calcium is a central regulator of differentiation and proliferation via transcription of cornification associated gene, including profilaggrin, and involucrin.[31,32] Elevated extracellular calcium concentration induces activation of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 induces calcium release from endoplasmic calcium stores by the activation of IP_3 receptors in ligand-dependent manner, and DAG directly activates TRPC6, one of the transient receptor potential (TRP) which regulates keratinocyte differentiation.[33] Recent study has described the possible dysfunction of TRPC6 in atopic dermatitis, and it is also attracting attention as a new therapeutic target,[34] suggesting that activation of TRPC6 by high calcium contained natural mineral dissolved water might be key player which improves barrier dysfunction in AD.

It has been described that various type of pruritogens and their specific receptors activate itch signaling.[35,36] The efficacy of emollients for treating pruritis in AD in both human and mice has been reported.[37,38] However, NRS was not changed through this clinical trial, indicating that bath treatment, even if using natural mineral dissolved water, did not affect itch associated signaling pathway. Therefore, further study would be needed to evaluate the efficacy of natural mineral dissolved water for pruritis in AD by long-time treatment or combination of topical application of emollient and/or steroid cream/ointment.

About the safety, no adverse events were reported by the investigators during this study period. Patil *et al*[39] reported the possibility of toxic effect of micro- and nano-particles of dolomite on respiratory system using lung epithelial cells A_{549} *in vitro*. In this study, Sangolite BATH SALT® were distributed to the subjects in individual packages and they were instructed to open the packages in the bathtub. Therefore, they did not have any chance to inhale the dolomite powder, in fact, none of the subjects developed respiratory symptoms.

Since there was no Phase I clinical trial which revealed the safety of Sangolite BATH SALT® in normal human, this study was designed with a small numbers of adults AD with mild severity to decrease the risk of adverse effect according to the request from IRB. Therefore, it would be required to examine randomized trial with large population, and more severe AD patient to confirm the result of this study.

Taken together, we demonstrated that balneotherapy using natural mineral dissolved water improved the severity of dermatitis and TEWL in adults with AD. Balneotherapy with natural mineral contained water might have possible therapeutic potential for disease that present with dry skin, including AD as alternative to moisturizers.

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CONFLICT OF INTEREST

This clinical trial was conducted in collaboration work among Department of Dermatology, Gunma University Graduate School of Medicine, Graduate School of Science and Technology, Gunma University, GUDi CO., Ltd, and Yamato Co., Ltd. Hideyuki Itabashi is Chairperson in GUDi CO., Ltd.

DECLARATION SECTION

Approval of the research protocol: This study was approved by the Institutional Review Board (IRB) of the Gunma University in August 2020 (IRB2020-018).

Informed Consent: All patients were provided written informed consent and ethics committees approved the protocol.

Registry and the Registration No. of the study/trial: UMIN000040220.

Animal Studies: N/A.

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