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A Pragmatic Randomized Controlled Trial on the Effectiveness of Highly Concentrated Saline Spa Water Baths Followed by UVB Compared to UVB Only in Moderate to Severe Psoriasis

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ABSTRACT

Background: There is a lack of sufficiently large randomized trials evaluating the effectiveness of saline spa balneophototherapy compared to ultraviolet B (UVB) only.

Objective: The study aimed to evaluate whether highly concentrated saline spa water baths followed by UVB (HC-SSW-UVB) are superior to UVB only in moderate to severe psoriasis.

Methods: One hundred and sixty (160) adults with a Psoriasis Area and Severity Index (PASI) of >10 from 4 German spa centers were randomly allocated to HC-SSW-UVB (local sodium chloride concentration between 25% and 27%) or UVB only 3 a week until remission (PASI < 5) or for a maximum of 6 weeks. Reduction of PASI ≥ 50% (PASI-50) at the end of the intervention period was defined as primary outcome. Only persons receiving at least 1 intervention were included into the primary analysis.

Results: Participants allocated to HC-SSW-UVB attained to a statistically significantly higher rate of PASI-50 than patients allocated to UVB only (68/79 [86%] versus 38/71 [54%]; $p < 0.001$; number needed to treat, 3.1; 95% confidence interval, 2.1–6.0). Postintervention analysis did not yield a clear hint of a persisting effect.

Conclusions: The study indicates that HC-SSW-UVB are superior to routine UVB at the end of a 6-week treatment course.

INTRODUCTION

Empirical evidence has accumulated over decades suggesting favorable effects of sun exposure combined with sea water (climatotherapy) for treating moderate to severe psoriasis.[1] However, because climatotherapy is bound to specific natural environments, balneophototherapy (BPT) has been developed in continental Europe to substitute the climatic conditions. In BPT, warm synthetic or natural salt water from local springs is combined with artificial ultraviolet B (UVB) in a simultaneous[2] or sequential[3] fashion.

There are only a few controlled trials with limited numbers of patients to date evaluating climatotherapy/BPT compared to sun exposure/UVB only in psoriasis. Three nonrandomized controlled trials indicated a superiority of climatotherapy[4] or BPT[5,6] over sun exposure/UVB only,

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whereas 2 current randomized controlled trials reported no,[7] or only a marginal benefit[8] of BPT with highly[7] or mid-concentrated salt water[8] compared to UVB only.

A systematic review on BPT in 2000 suggests that BPT is probably superior to UVB only, whereas its efficacy seems not to depend significantly on salt concentration or mineral composition.[9]

Here we present a randomized controlled trial evaluating the overall effectiveness of highly concentrated saline spa water baths followed by UVB (HC-SSW-UVB) compared to UVB only.

METHODS

Study design

This is a multicenter, open, randomized controlled clinical trial in a 2-group parallel configuration with a 3- and 6-months postintervention follow-up in patients with stable, moderate to severe psoriasis. The study was designed as a pragmatic trial to better meet the information needs for decision makers (consumers, clinicians, and health care policy makers).[10] Both interventions considered in this study are alternative clinical strategies frequently used in routine clinical practice in Germany.

Study participants were externally randomized to HC-SSW-UVB or UVB via a central telephone hotline. One computer-generated randomization list with blocks of 12 masked to the site investigators was prepared for each of the participating spa centers. Allocation concealment was broken just before the first intervention was administered. The ethics committee at the University of Ulm approved the study protocol.

Participants

Patients with psoriasis without substantial changes during the last month and a Psoriasis Area and Severity Index (PASI) of >10 and/or an involvement of $>15\%$ of the total body surface area were included into the study. Excluded were patients younger than 18, pregnant or breast-feeding women, persons with malignant hypertension, coronary heart disease, heart failure, arrhythmia, or a history of malignancies. Furthermore, patients currently on photosensitizing agents or on medications negatively affecting psoriasis were also not considered. The washout period for systemic antipsoriatric agents was 4 weeks, and for topical antipsoriatic agents it was 2 weeks. Patients who received phototherapy 4 weeks prior to study entry were not eligible.

Setting

Study participants were recruited from 4 spa centers. Study participants were outpatients living in the respective spa town or within a radius of 50 km from the spa.

Eligibility checking, clinical examination, assessment of sociodemographic parameters, and outcome measures were performed by the study dermatologists at their respective clinics, whereas interventions were administered at the spa centers by trained phototherapists, who also collected data on UVB dose and erythemal response.

Interventions

Two spa centers provided narrowband UVB (311 nm), while the remainder provided selective ultraviolet phototherapy (SUP) (300–320 nm) or broadband UVB (280–320 nm).

Sodium chloride concentrations of local springs varied between 25% and 27%. Magnesium ions should not exceed 2.9 g/L.

Minimal erythema dose (MED) was assessed before the start of treatment by exposing 6 uninvolved and untanned skin templates of an area of 2 cm^2 each to incremental doses of .01 to .10 J/cm^2 (broadband-UVB and SUP) or .2 to 1.2 J/cm^2 (narrowband UVB).[11] Patients assigned to HC-SSW-UVB soaked their test body sites in saline spa water before they were phototested.

After phototesting, patients assigned to HC-SSW-UVB took a 20-minute whole body saline spa water bath with a temperature of 37°C prior to UVB irradiation. Patients were allowed to dab off but not to wipe their skin after bathing. Within 10 minutes after bathing, patients were irradiated with UVB. Patients assigned to UVB took no bath.

Starting dose was 50% of MED (visit 1). For broadband UVB or SUP UVB, the dose was increased by 25% of MED from visit 2 to 10, afterward by 10% of MED. For narrowband UVB, the dose was uniformly increased by 10% of MED.[11] UVB dose was adapted to erythemal response according to a standardized protocol.[11] Patients were treated 3 times a week until remission (PASI <5) or for a maximum of 6 weeks (18 sessions).

The use of systemic antipsoriatrics such as cyclosporin, methotrexate, retinoids, or fumaric acid esters or topical ointments such as corticosteroids, vitamin D_3-analogues, anthralin, or tar was disapproved.

Outcome measures

Primary outcome measure was PASI-50. PASI-50 was defined as a reduction of $\geq 50\%$ of PASI or involved body surface area occurring during the intervention period (PASI-50).[12] Secondary outcomes were PASI-75 ($\geq 75\%$ reduction of PASI or involved body surface area), and S-PASI-50. S-PASI (self-administered Psoriasis Area and Severity Index) is the patients' self-rated analogue to the clinician-rated PASI and is scored and interpreted as the PASI.[13]

PASI and S-PASI were assessed at baseline, after 2 weeks, after 4 weeks, and at the end of the intervention period (maximum: 6 weeks), but S-PASI was also assessed 3 and 6 months postintervention.

At each treatment session, erythemal response, adverse events, and irradiation dose were recorded.

Blinding

Blinding of the participants was not possible due to the nature of the interventions.

Blinding of PASI raters was intended. The study center did not inform the dermatological clinics about treatment allocation. Only the phototherapists at the spa centers knew the treatment allocation. Both patients and phototherapists were instructed not to inform the PASI raters about treatment allocation. Success of observer blinding was evaluated at the end of the intervention period by a questionnaire.

Sample size

We assumed a 75% rate of PASI-50 at the end of the intervention period in the UVB group.[4] An increase of at least 12%–15% of HC-SSW-UVB compared to UVB only was judged clinically relevant and should be detectable within the study. Given these assumptions, a 2-sided type I error of 5%, balanced groups, and a test power between 71% and 91%, 150 patients per group should be included into the study.

Because accrual rate declined to zero after a 3-year running phase, we draw a random sample of 100 patients to recalculate sample size. Since PASI-50 rate was clearly lower (54%) and effect size clearly higher (35%) than planned, we terminated the study prematurely at a total sample size of 160 randomized patients.

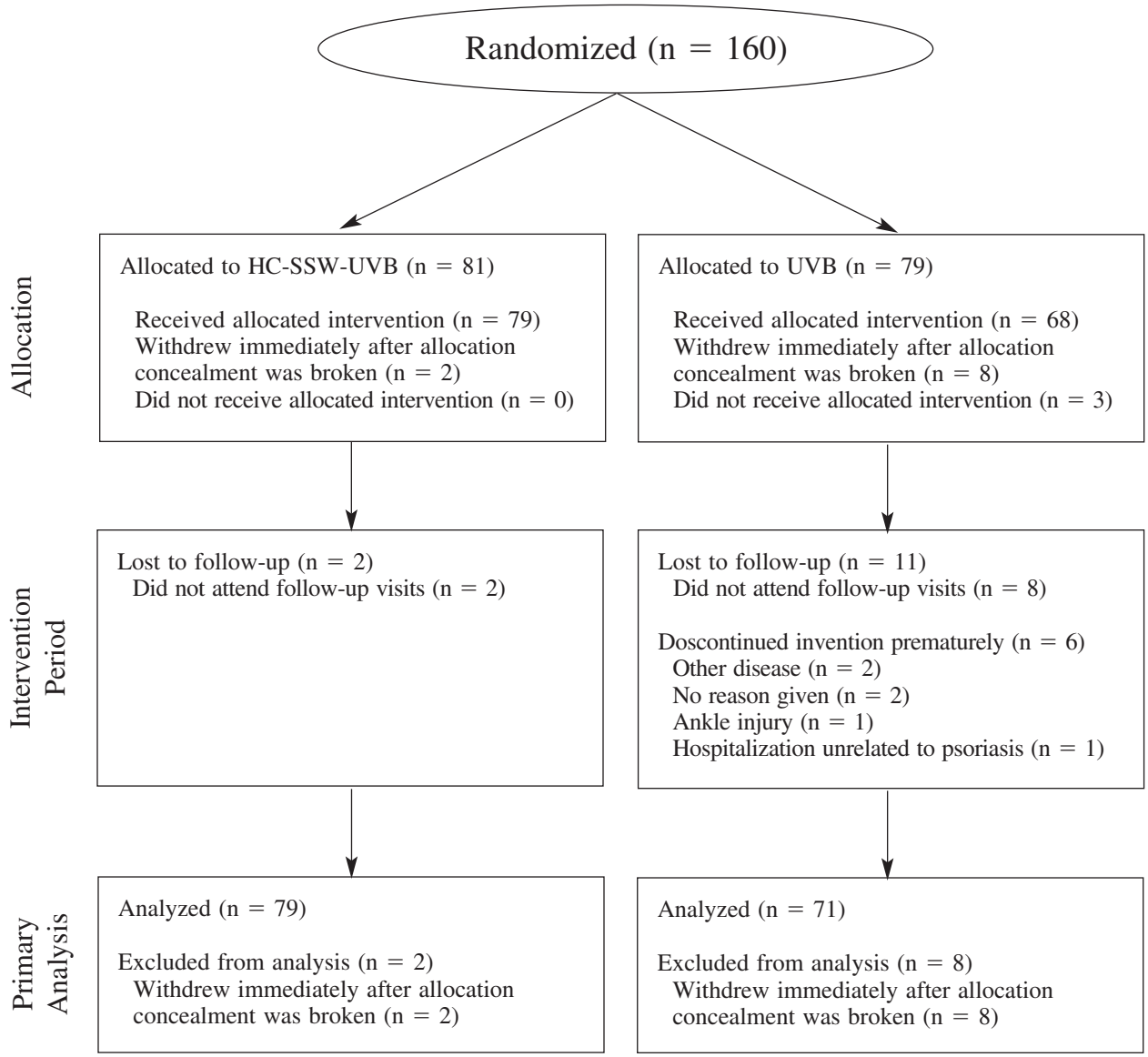

FIG. 1. Flow of participants through the study. HC-SSW-UVB, highly concentrated saline spa water baths prior to UVB; UVB, ultraviolet B.

Statistical methods

All patients receiving at least 1 intervention were included into the primary analysis. Missing values at the end of intervention were replaced according to the last visit observation carried forward strategy (LVOCF).

Primary analysis was done by Fisher's exact test. Additionally, the number needed to treat (NNT) with the corresponding confidence interval was calculated. *p*-Value and confidence interval of NNT were adjusted by $\alpha/2$ due to the nonplanned interim analysis.

Secondary analyses, including per protocol analysis, were also performed by Fisher's exact test. No statistical adjustments for multiple testing, and no replacement strategies for missing data were applied for secondary analyses.

Individual subgroup analyses were performed on light source and blinding status. Effects were described by absolute benefit increase (experimental event rate minus control event rate) (ABI). Subgroup–treatment interactions were tested by logistic regression.

RESULTS

Patient flow

The running phase of the study started in August 2001 and was terminated in April 2005. During the course of the study, the monthly accrual rate declined from 9 patients per month on average within the first year to no further recruitment within the last 8 months before study termination. Average accrual per month was 3.6 patients.

One hundred and sixty (160) participants were randomized. Ten persons (2 assigned to HC-SSW-UVB, 8 assigned to UVB) withdrew from the study immediately after allocation concealment was broken. They received no intervention at all, did not attend any follow-up visit, and were not included into the primary analysis (Fig. 1).

Baseline data

Study groups were well balanced on baseline characteristics except for previous systemic antipsoriatic agents (Table 1) ($chi^2 = 4.6$, $df = 1$, $p = 0.36$). When fitting a logistic regression, neither previous systemic antipsoriatic agents ($p = 0.42$) nor their interaction with intervention ($p = 0.37$) proved to be predictors of treatment response.

Protocol adherence

Three patients assigned to UVB received HC-SSW-UVB (Fig. 1). Mean number of interventions was 17.8 (standard deviation [SD] 0.5) in the HC-SSP-UVB-group and 17.1 (SD 2.4) in the UVB group. Fewer treatment sessions than planned (<15 sessions), not yet as a consequence of early success, were only found in the UVB group with a frequency

Table 1. Baseline Patient Characteristics at Study Enrollment

Characteristics	*HC-SSW-UVB* (n = *81*)	*UBV* (n = *79*)	*Total* (n = *160*)
Female, no. (%)	33 (41)	28 (38)	61 (40)
	n = 80	*n* = 73	*n* = 153
Age, mean (SD), years	47.5 (14.2)	49.0 (13.7)	48.2 (14.0)
	n = 79	*n* = 73	*n* = 152
Current smoker, no. (%)	21 (26)	22 (31)	43 (28)
	n = 80	*n* = 72	*n* = 152
Duration of current flare <1 year, no. (%)	35 (47)	32 (50)	67 (48)
	n = 75	*n* = 64	*n* = 139
Skin type according Fitzpatrick, no. (%)			
Type I	2 (3)	2 (3)	4 (3)
Type II	4 (5)	8 (11)	12 (8)
Type III	59 (76)	49 (66)	108 (70)
Type IV	13 (17)	15 (20)	28 (18)
	n = 78	*n* = 74	*n* = 152
PASI Score (0–72), median (interquartile range)	17 (13–22)	16 (13–21)	16 (13–21)
	n = 80	*n* = 73	*n* = 153
Any experience of former phototherapy, no. (%)	66 (83)	60 (81)	126 (82)
	n = 80	*n* = 74	*n* = 154
Previous systemic antipsoriatic agents, no. (%)	30 (38)	16 (22)	46 (30)
	n = 80	*n* = 74	*n* = 154
History of inpatient care because of psoriasis, no. (%)	42 (56)	36 (49)	78 (53)
	n = 75	*n* = 73	*n* = 148

HC-SSW-UVB, highly concentrated saline spa water baths prior to UVB; UVB, ultraviolet B; SD, standard deviation; PASI, Psoriasis Area and Severity Index.

of 7% (5/68). Starting dose was in accordance with the study protocol (±20% of target) in 97.2% (141/145). Deviations from incremental regimen in more than half of the treatment sessions were found in 13% of the persons (10/79) allocated to HC-SSW-UVB compared to 14% (10/71) allocated to UVB. Average treatment period was 6.6 weeks (SD 1.2).

UVB spectrum

Sixty percent (60%) of the participants (87/146) were irradiated with narrowband UVB, 30% with SUP (44/146), and 10% (15/146) with broadband UVB.

Rater blinding

PASI raters stated that they knew the treatment allocation in 42% of cases (60/142).

Primary analysis

In 2 cases, missings were imputed according to LVOCF (UVB).

At the end of the intervention period, patients allocated to HC-SSW-UVB had a statistically significantly higher PASI-50 rate than patients allocated to UVB (68/79 [86%] versus 38/71 [54%]; $p < 0.001$; NNT 3.1, 95% CI, 2.1–6.0).

Secondary analyses

Analyses at the end of the intervention period confirmed the results of the primary analysis (Table 2). However, patients rated clinical benefit about by half lower than clinicians (ABI: 15% [S-PASI-50] versus 32% [PASI-50]). Analyses 3 and 6 months after cessation of treatment did not result in a significant superiority of HC-SSW-UVB compared to UVB, although a borderline significance could be observed 3 months postintervention in favor of HC-SSW-UVB ($p = 0.08$).

Subgroup analyses

Irradiation spectrum. Patients irradiated by narrowband UVB obtained a higher absolute benefit increase (ABI = 35%; n = 87) compared to patients irradiated by conventional UVB (broadband UVB or SUP) (ABI = 27%; n = 59). In logistic regression, neither main effect ($p = 0.30$) nor subgroup–treatment interaction ($p = 0.13$) yielded significant effects.

Blinding status. For the subgroup of patients the PASI raters stated that they did not know treatment allocation, ABI was 24% (n = 82), whereas for the group of patients the PASI raters stated that they knew the treatment allocation, ABI was 36% (n = 60). Subgroup–treatment interaction was

Table 2. Secondary Analyses

	Comparison			
	HC-SSP-UVB	*UVB*	p *value*[a]	*NNT (95% CI)*
Based on PASI				
Per protocol analysis[b]				
No. of patients	66	47		
PASI-50, no. (%)	62 (94)	27 (57)	<0.001	2.7 (1.9; 4.7)
PASI-75, end of intervention				
No. of patients	78	66		
PASI-50, no. (%)	45 (58)	22 (33)	0.004	4.1 (2.5; 11.7)
Based on S-PASI				
S-PASI-50, end of intervention				
No. of patients	77	67		
PASI-50, no. (%)	65 (84)	46 (69)	0.03	6.3 (3.4; 49.7)
S-PASI-50, 3-months postintervention				
No. of patients	73	61		
PASI-50, no. (%)	44 (60)	27 (44)	0.08	6.0 (3.1; −131.1)
S-PASI-50, 6-months postintervention				
No. of patients	66	59		
PASI-50, no. (%)	32 (49)	29 (49)	1.0	149.8 (5.5; −5.9)

HC-SSW-UVB, highly concentrated saline spa water baths followed by UVB; NNT, number needed to treat; CI, confidence interval; PASI-50, reduction of Psoriasis Area and Severity Index or involved body surface area ≥50%; PASI-75, reduction of Psoriasis Area and Severity Index or involved body surface area ≥75%; S-PASI-50, reduction of Self-Administered Psoriasis Area and Severity Index or involved body surface area ≥50%; UVB, ultraviolet B.

[a]Fisher's exact test.

[b]The following criteria set has to be fulfilled: (1) conformance with treatment allocation; (2) total number of treatments within ±20% of target; (3) starting dose within ±20% of target; (4) deviations from incremental regimen in not more than 50% of the treatment sessions; and (5) total treatment period not longer than 9 weeks.

not statistically significant (p: 90), but main effect reached a p value of 0.10.

Safety

For conventional UVB, the cumulative dose was 2.7 J/cm^2 (SD 0.8) in the HC-SSP-UVB group, and 2.8 J/cm^2 (SD 0.8) in the UVB group. For narrowband UVB, the respective cumulative doses were 20.7 J/cm^2 (SD 5.9) (HC-SSW-UVB), and 19.1 J/cm^2 (SD, 7.8) (UVB). Adverse events (dermatitis solaris) were reported in 3 persons (HC-SSW-UVB: n = 2; UVB: n = 1).

DISCUSSION

Our study demonstrates that HC-SSW-UVB are superior to UVB at the end of a 6-week treatment period. Postintervention analysis did not yield a clear hint of a persisting effect.

Two findings indicate that observer bias might have led to an overestimation of effect. First, individual subgroup analysis on blinding status yielded a better clinical benefit in the group of patients for whom PASI raters knew the treatment allocation. But logistic regression indicates that this effect was not dependent on type of intervention ($p = 0.90$). Second, clinical benefit was about halved when outcome was assessed by the patients. Nonetheless, patients' rating yielded a significant ($p = 0.03$) and clinically relevant benefit (ABI = 15%), indicating that observer bias did not contribute alone to the observed effect.

We did not enforce any straightforward intention-to-treat analysis based on various missings imputations for those 10 persons who discontinued immediately after allocation was broken (Fig. 1). A worst-case scenario setting the two experimental missings on failure and the 8 control missings on success (n = 8) does not affect the result of the primary analysis.

Subgroup analysis by irradiation spectrum indicates that patients irradiated by narrowband UVB might have attained a better clinical benefit compared to patients irradiated by conventional UVB. Even though this findiing can only be interpreted descriptively it is surprising, because evidence suggests that narrowband UVB is superior to broadband UVB,[14,15] and a superior treatment might reduce the capability of any additional treatment.

At baseline, our study participants had a median PASI score of 16 (interquartile range: 13–21). Patients of this disease severity are also likely candidates for systemic antipsoriatrics.[16] Furthermore, therapeutic benefit of HC-SSW-UVB is comparable to those obtained by Heydendael and coworkers for methotrexate and cyclosporine when considering a treatment period of 6 weeks.[16] But compared to HC-SSW-UVB, systemic antipsoriatrics bear a clearly higher risk of severe side-effects, but data on direct comparisons are still lacking.

In our study, MED and cumulative UVB exposure did not differ between HC-SSW-UVB and UVB, a finding also reported in another randomized controlled trial on highly concentrated spa BPT in France.[7] This implies that different irradiation doses due to different photosensitivity are unlikely to be responsible for the better therapeutic benefit of HC-SSW-UVB compared to UVB.

Two evaluator-blind randomized controlled trials on highly or midconcentrated salt water BPT showed no[7] or only a marginal additional benefit of BPT compared to UVB only.[8] One might argue that the difference in effect results from the fact that PASI raters in our trial were only partly blinded. However, in the abovementioned studies, success of blinding has not been evaluated, and evidence suggests that even in placebo-controlled trials, success of blinding is often poor.[17] A more reasonable explanation for the difference in effect might be that our patients suffered from a less stable disease ("stable psoriasis for at least 1 month") compared to the populations considered in the other trials ("stable psoriasis of more than 1 year's duration").

Psoriasis therapies are often associated with short-term effects if not followed by maintenance therapy. In our trial, superiority of HC-SSW-UVB compared to UVB was partially lost at 3 months (borderline significance) and disappeared completely at 6 months. However, about half of the patients still reported a reduction of S-PASI of ≥50% at 6 months in both groups. Evidence based on a narrative review suggests that more long-term effects can be attained by phototherapies combined with anthralin (Ingram regimen) or tar (Goeckerman regimen) and psoralen-ultraviolet A-photochemotherapy (PUVA) compared to BPT.[28] Perhaps bath-PUVA also is more effective than BPT. However, head-to-head comparisons with standardized definitions of remission/relapse are necessary to obtain conclusive results.[18]

Mechanisms have been proposed for highly concentrated salt water,[19] salt components other than sodium chloride, including magnesium,[20–23] and increase in photosensitivity by salt water exposure prior to UVB irradiation.[5,24,25] In the context of our study, the elution of the enzyme human leukocyte elastase by highly concentrated sodium chloride solutions might be a possible etiologic factor for the observed effect.[19]

Like many multicenter trials, this study was subject to some pragmatic constraints. To ensure a sufficiently high sample, we had to include spa centers differing in the provision of the irradiation source. In addition, local springs vary in mineral composition. Thus, we cannot conclude directly from this study whether saline water baths followed by UVB work better with narrowband or conventional UVB nor on the therapeutic benefit of a specific local spring.

A current trial on bath-PUVA and highly concentrated synthetic saline BPT conduction in a similar design showed that bath-PUVA and synthetic saline BPT were superior to tap water BPT.[26] This suggests that the results of our trial are not only due to hydration.

Future studies should address cost-effectiveness and long-term risk of BPT compared to oral PUVA and systemic antipsoriatrics.

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