Indoor balneophototherapy for chronic plaque psoriasis: Abridged Cochrane Review

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ORIGINAL ARTICLE

Indoor balneophototherapy for chronic plaque psoriasis: Abridged Cochrane Review

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Abstract

Artificial exposure to ultraviolet B light (UVB) while soaking in an indoor salt bath, also called balneophototherapy, could simulate the natural exposure to the sun while bathing in the Dead Sea. We aimed to assess the effects of this intervention on patients with chronic plaque psoriasis. We searched CENTRAL, MEDLINE, Embase, and LILACS up to June 2019. We included randomized controlled trials (RCTs). The primary efficacy outcome was psoriasis area and severity index (PASI)-75 to detect people with a 75% or more reduction in the PASI score from baseline. The primary adverse outcome was treatment-related adverse events requiring withdrawal. We included eight RCTs (2105 participants; 1976 analyzed). With respect to PASI-75, two studies found that salt bath + UVB may improve psoriasis when compared to UVB alone (risk ratio 1.71, 95% confidence interval 1.24 to 2.35; 278 participants). With respect to treatment-related adverse events requiring withdrawal, two other studies found little to no difference when compared to UVB alone (risk ratio 0.96, 95% confidence interval 0.35 to 2.64; 404 participants). Salt bath + UVB could improve psoriasis when compared to UVB alone, though, results are based on a limited number of studies and provide low-certainty evidence.

KEYWORDS

artificial ultraviolet B-light, balneophototherapy, balneotherapy, chronic plaque psoriasis, salt water treatment, systematic review

1 | INTRODUCTION

Psoriasis is a multifactorial, immune-mediated chronic inflammatory skin disease.[1] Chronic plaque psoriasis, which is also known as psoriasis vulgaris, is the most common type of psoriasis, affecting 80% to 90% of people with psoriasis.[2,3] Red-colored lesions, also known as plaques, are the result of an inflammatory and hyperproliferative epidermis.[1] The extent of the affected body surface area may be used to classify the severity as mild (less than 5%), moderate (5% to 10%), or severe (greater than 10%).[4] The main symptoms are itching and pain associated with uncomfortable scaling because of loss of cells from the epidermal layer of the skin.[5]

Indoor salt bath followed by artificial ultraviolet B light (UVB) was developed to simulate the natural exposure to salt water and sunlight at

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the Dead Sea.[6] For example, the whole body is soaked in salt water for 15 to 30 minutes, which may have various concentrations of sodium chloride resolved in 1 L water. The soaking is repeated several times a week for a total of 20 to 30 applications within a time period of 8 weeks. After bathing, various doses of UVB are applied to the whole body.[7] The combination of bathing in salt water with UVB bathing thereafter, called balneo-phototherapy,[8] could improve patients with psoriasis.[9] Although indoor salt water bath and UVB is used in practice to treat chronic plaque psoriasis, no Cochrane Review has been conducted to assess its effects for reducing skin lesions and improving quality of life. Thus, we aimed to evaluate the beneficial and adverse effects of indoor salt water bath followed by artificial UVB for chronic plaque psoriasis.

2 | METHODS

This article is an abridged version of a Cochrane Review published in The Cochrane Library.[10] While preparing this systematic review, we endorsed the PRISMA statement, adhered to its principles and conformed to its checklist.[11]

2.1 | Inclusion criteria

Table 1 details the included criteria and delineates those from the criteria not considered in the present review. We included between-participant data from parallel-group designs as well as within-participant data from paired body parts designs. In general, within-participant studies apply the intervention to a body part such as a limb and the comparator to a different body part such as the opposite limb (eg, right arm vs left arm). Consequently, we separately analyzed between-participant data and within-participant data.

2.2 | Search strategy

Table 2 details the search strategies. We conducted an electronic literature database search on June 4, 2019 without applying any limits in the Skin Group Specialized Register (CRS), the Cochrane Central Register of Controlled Trials (CENTRAL) 2019, Issue 6 in the Cochrane Library, MEDLINE via Ovid (from 1946), Embase via Ovid (from 1974), and LILACS (Latin American and Caribbean Health Science Information database, from 1982). The strategies of the electronic searches including online trials registers and other sources are provided with the original Cochrane Review.[10]

2.3 | Selection of studies

Figure 1 shows the literature search and study flow. We downloaded all titles and abstracts retrieved by electronic searching to an Excel spreadsheet (Microsoft Corp 2011) and removed any duplicates. We excluded those studies that clearly did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Two review authors independently assessed the eligibility of retrieved papers.

2.4 | Assessment of risk of bias in included studies

Two authors independently appraised the risk of bias of the included studies. We used the items listed within Cochrane's tool for assessing risk of bias,[12] shown in Table 3. In general, a judgment of "low risk" of bias was given if plausible bias is unlikely to seriously alter the results, for example, if the participants and investigators enrolling those participants could not foresee the assignment. A judgment of "high risk" of bias was given if plausible bias seriously weakens confidence in the results, for example, if the participants or investigators enrolling those participants could possibly foresee the assignments. A judgment of "unclear" risk of bias was given if plausible bias raises some doubt about the results, for example, the method of concealment is not described or not described in sufficient detail to allow a definite judgment.

2.5 | Measures of treatment effect

For dichotomous outcomes, we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients at the time point of outcome assessment to estimate a risk ratio. We conducted a meta-analysis applying the Mantel-Haenszel method, the random effects model, and the risk ratio as the effect measure. We did not include continuous data as well as time-to-event data.

2.6 | Dealing with missing data

Two of eight included studies reported the primary beneficial outcome PASI-75. The other six included studies did not report any psoriasis area and severity index (PASI)-associated outcome, or they reported aggregate data on PASI, such as mean PASI, PASI-50 or relative PASI reduction. It is not possible to deduce PASI-75 from those aggregate data, but it is possible to calculate PASI-75 from individual data. Therefore, we sent e-mail requests to the authors of all included studies to send us individual data.

2.7 | Assessment of heterogeneity

We assessed heterogeneity (composed of dissimilar parts) between studies by visual inspection of forest plots and by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (I^2 statistic).[13] An I^2 statistic greater than 50% was considered to indicate substantial heterogeneity, demonstrating a considerable variation in results. In this case, we planned to present the graphical display of a forest plot, but we did not plan to report an average value for the intervention effect.

TABLE 1 Inclusion criteria

Criteria	Sub-criteria	Included (reported by)	Not considered (reported by)
Types of studies	—	Randomized controlled trials (RCTs) including: Parallel group design[a]; paired body parts receive different interventions[b]; cluster-randomized trials	Crossover design; multiple body parts receive the same intervention; comparison of different body parts within participants
Types of participants	—	Adults (ie, 18 years of age or older) who have been diagnosed with chronic plaque type psoriasis	People with pustular psoriasis, guttate psoriasis, or inverse psoriasis
Types of interventions	Comparison #1[c]: Test Comparison #2[d]: Test	Exposure to indoor salt water bath followed by artificial ultraviolet B light (UVB)	Bathing in outdoor salt water and for leisure purposes, such as bathing in geothermal sea water, thermal lagoon, or in a salty lake
—	Comparison #1[c]: Control	Exposure to psoralen bath, psoralen bath + artificial ultraviolet A light (UVA), topical treatment, systemic treatment, or placebo	—
—	Comparison #2[d]: Control	Exposure to bath containing other compositions or concentrations + UVB or UVB only.	—
Types of outcome measures	Primary beneficial outcome	PASI-75 (Brockow 2007a; Brockow 2007b) PASI is a measure of average redness, thickness, and scaliness of skin lesions weighted by the area of involvement. PASI-75 is the percentage of people or limbs who have achieved a 75% or more reduction in their PASI score from baseline.	PASI (Arnold 2001; Klein 2011; Leaute-Labreze 2001) PASI-50 (Brockow 2007a; Brockow 2007b; Schiener 2007) Clearance of psoriatic lesions scores (Dawe 2005; Gambichler 2001)
—	Primary adverse outcome	Treatment-related adverse events requiring withdrawal (Dawe 2005; Klein 2011; Leaute-Labreze 2001)	Treatment-related adverse events (Arnold 2001; Brockow 2007a; Brockow 2007b; Dawe 2005; Gambichler 2001; Klein 2011; Leaute-Labreze 2001; Schiener 2007)
—	Secondary outcomes	Dermatology life quality index (DLQI) Pruritus severity using a visual analogue scale (VAS) from 0 ("no itching") to 100 ("severe itching") Time to relapse Secondary malignancies	Global rating of disease severity, treatment effect, or tolerability by patients (Brockow 2007b; Schiener 2007) Self-administered PASI (S Brockow 2007b; Schiener 2007) Psoriasis disability index (Klein 2011) Sickness impact profile (Klein 2011) Improvement of physical complaints, global health total, global health skin only of Freiburg Life Quality Assessment (Klein 2011) Global impression of therapy (Klein 2011)

Abbreviations: PASI, Psoriasis Area and Severity Index.
[a]Parallel group design: The parallel group design creates between-participant data. The participants are individually randomized to one of two (or more) intervention groups, and a single measurement for each outcome (and each comparison) from each participant is collected and analyzed.
[b]Paired body parts: The paired comparison creates within-participant data. Paired refers to a body part that is present on both sides of the body. We considered multiple observations for the same outcome, specifically, multiple body parts receive different interventions, such as comparisons of right vs left arm.
[c]Comparison #1: Salt water bath plus UVB vs other treatment without UVB.
[d]Comparison #2: Salt water bath plus UVB vs other treatment plus UVB or UVB only.

2.8 | Summary of findings tables and GRADE assessments

Table 4 lists the predefined two primary outcomes. For each outcome, two review authors independently assessed the certainty of the evidence by using the five GRADE considerations, that is, study limitations, inconsistency, indirectness, imprecision, and publication bias as described in the Cochrane Handbook for Systematic Reviews of Interventions.[14]

3 | RESULTS

3.1 | Results of the search

Figure 1 shows the literature search and study flow. We included six randomized controlled trials (RCTs)[15-22] associated with 11 records. One additional record[23] could be an eligible study for inclusion in a future update. The results and full description of the methods of the study were not available.

TABLE 2 Search strategies

Database	Strategy
1 Skin Group Specialized Register (CRS) search strategy	Psoria* and (((balneotherapy or balneo-therapy or soak* or bath* or salt* or dead sea or sole$ or saline) and (phototherapy* or ultraviolet or UVB or uv-b or uv light)) or balneophototherapy or balneo-phototherapy)
2 CENTRAL (Cochrane Library) search strategy	#1: MeSH descriptor: [Psoriasis] explode all trees #2: psoria*:ti,ab,kw #3: #1 or #2 #4: soak*:ti,ab,kw #5: (balneotherapy or balneo-therapy):ti,ab,kw #6: bath*:ti,ab,kw #7: (salt* or dead sea or saltwater or sole* or saline):ti,ab,kw #8: MeSH descriptor: [Baths] explode all trees #9: {or #4-#8} #10: MeSH descriptor: [Phototherapy] explode all trees #11: phototherap*:ti,ab,kw #12: MeSH descriptor: [Ultraviolet Therapy] explode all trees #13: (ultraviolet or UVB or uv-b):ti,ab,kw #14: uv light:ti,ab,kw #15: MeSH descriptor: [Ultraviolet Rays] explode all trees #16: (TL01 or TL-01 or 311-nm):ti,ab,kw #17: {or #10-#16} #18: #9 and #17 #19: balneophototherapy:ti,ab,kw #20: balneo-phototherapy:ti,ab,kw #21: #18 or #19 or #20 #22: #3 and #21
3 MEDLINE (Ovid) search strategy	1. exp Psoriasis/ 2. psoria$.mp. 3. 1 or 2 4. soak$.mp. 5. (balneotherapy or balneo-therapy).mp. 6. bath$.mp. 7. (salt$ or dead sea or saltwater or sole$ or saline).mp. 8. Baths/ 9. or/4-8 10. exp Phototherapy/ 11. phototherap$.mp. 12. exp Ultraviolet Therapy/ 13. (ultraviolet or UVB or uv-b).mp. 14. uv light.mp. 15. Ultraviolet Rays/ 16. (TL01 or TL-01 or 311-nm).mp. 17. or/10-16 18. 9 and 17 19. balneophototherapy.mp. 20. balneo-phototherapy.mp. 21. 18 or 19 or 20 22. randomized controlled trial.pt. 23. controlled clinical trial.pt. 24. randomized.ab. 25. placebo.ab. 26. clinical trials as topic.sh. 27. randomly.ab. 28. trial.ti. 29. 22 or 23 or 24 or 25 or 26 or 27 or 28 30. exp animals/ not humans.sh. 31. 29 not 30 32. 3 and 21 and 31 [22-31: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]
4 Embase (Ovid) search strategy	1. exp psoriasis/ 2. psoria$.mp. 3. 1 or 2

TABLE 2 (Continued)

Database	Strategy
	4. soak$.mp. 5. (balneotherapy or balneo-therapy).mp. 6. exp balneotherapy/ 7. exp bath/ 8. bath$.mp. 9. (salt$ or dead sea or saltwater or sole$ or saline).mp. 10. or/4-9 11. exp phototherapy/ 12. phototherap$.mp. 13. (ultraviolet or UVB or uv-b).mp. 14. uv light.mp. 15. exp ultraviolet radiation/ 16. (TL01 or TL-01 or 311-nm).mp. 17. or/11-16 18. 10 and 17 19. balneophototherapy.mp. 20. balneo-phototherapy.mp. 21. 18 or 19 or 20 22. crossover procedure.sh. 23. double-blind procedure.sh. 24. single-blind procedure.sh. 25. (crossover$ or cross over$).tw. 26. placebo$.tw. 27. (doubl$ adj blind$).tw. 28. allocat$.tw. 29. trial.ti. 30. randomized controlled trial.sh. 31. random$.tw. 32. or/22-31 33. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ 34. human/ or normal human/ 35. 33 and 34 36. 33 not 35 37. 32 not 36 38. 3 and 21 and 37
5 LILACS search strategy	psoria$ and (balneotherapy or balneo-therapy or balneophototherapy or balneo-phototherapy or salt$ or saline or bath$ or bano) These terms searched with the Controlled clinical trials topic-specific query filter.

3.2 | Baseline data

Table 5 provides an overview of the main characteristics of the types of comparisons, designs, participants, interventions, and outcome assessments of the included studies. We included eight RCTs: six reported between-participant data (2035 participants; 1908 analyzed),[15-17,20-22] and two reported within-participant data (70 participants, 68 analyzed; 140 limbs; 136 analyzed).[18,19] Five studies reported any of our pre-specified primary outcomes, and none reported on the predefined secondary outcomes. Total trial duration ranged between at least 2 months and up to 13 months. The mean age of the participants ranged from 41 to 50 years of age in 75% of the studies. Treatments were applied once a day, three to 5 days a week, for up to 8 weeks, and reaching a maximum number of 15 to 35 applications. Body parts were soaked for 15 to 30 minutes in salt water with a concentration ranging from 0.8 to 250 g/L. Five studies[16,17,20-22] reported cumulative UVB doses, ranging from 11.8 to 50.7 J/cm^2 for narrowband UVB and 2.7 to 5.2 J/cm^2 for broadband UVB, respectively.

3.3 | Primary outcomes

The results on PASI-75 response favored indoor saltwater baths followed by artificial UVB for chronic plaque psoriasis. We estimated a risk ratio of 1.71 with a 95% confidence interval ranging from 1.24 to 2.35 and a *P*-value of .0009 based on the data of 278 participants reported in two studies with between-participant data[16,17] (Table 4; Figure 2). Due to the nature of this measurement (ie, the number of patients with a PASI-75

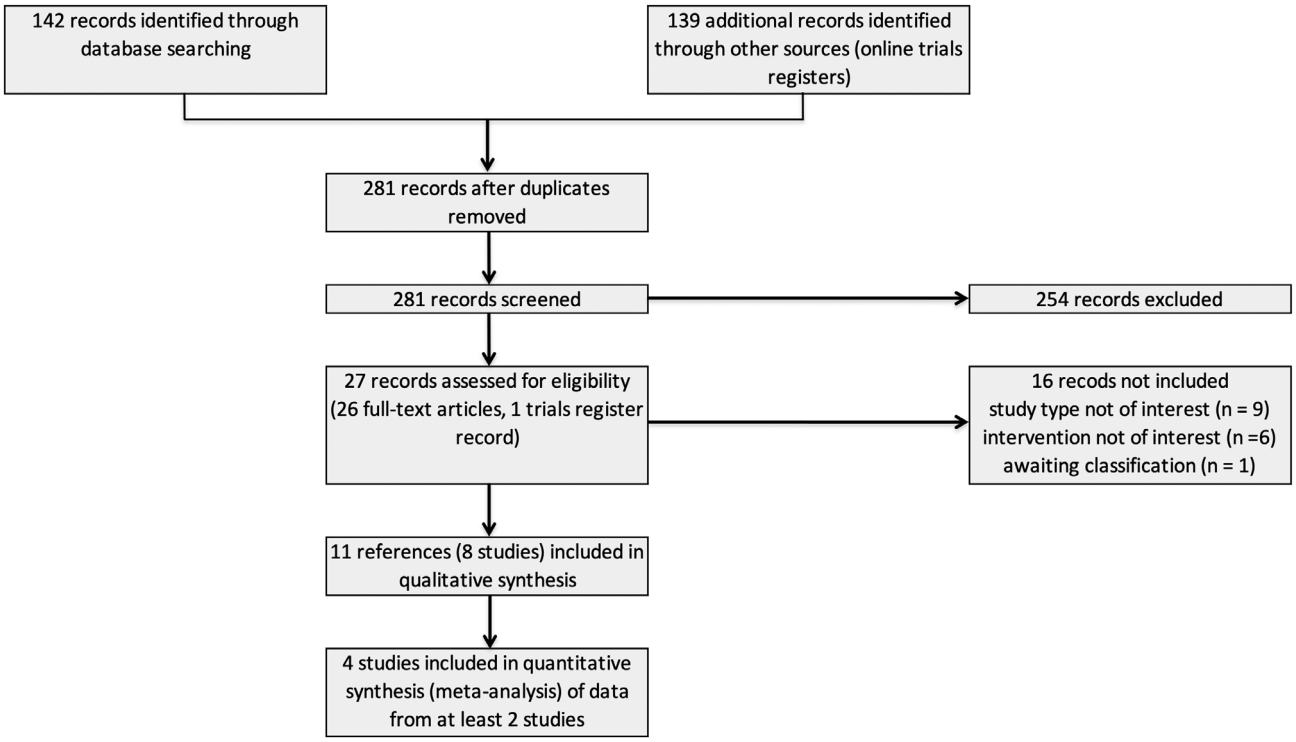

FIGURE 1 Literature search and study flow

TABLE 3 Assessment of risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Meta-analysis
Arnold 2001	Unclear	Unclear	High	High	High	Unclear	Unclear	
Brockow 2007a	Low	Low	High	Low	Low	Unclear	Unclear	Yes
Brockow 2007b	Low	Low	High	Unclear	High	Unclear	Unclear	Yes
Dawe 2005	Low	Low	Unclear	Unclear	High	Unclear	Unclear	
Gambichler 2001	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear	
Klein 2011	Low	Low	High	High	Unclear	Unclear	Unclear	Yes
Leaute-Labreze 2001	Low	Low	High	Low	Unclear	Unclear	Unclear	Yes
Schiener 2007	Low	Low	High	Low	Unclear	Unclear	Unclear	

response), a high event rate is favorable. The results on treatment-related adverse events requiring withdrawal did not favor any treatment. We estimated a risk ratio of 0.96 with a 95% confidence interval ranging from 0.35 to 2.64 and a *P*-value of .94 based on the data of 404 participants reported in two studies with between-participant data[20,21] (Table 4, Figure 3). We also estimated a risk ratio of 0.50 with a 95% confidence interval ranging from 0.05 to 5.36 and a *P*-value of .57 based on the data of 116-paired body parts reported in one study with within-participant data.[18]

TABLE 4 Grading the evidence

Primary outcomes	Assumed risk with comparator (study population)	Corresponding risk with intervention (study population)	Relative effect (95% CI)	N of participants (studies)	Certainty of evidence (GRADE)
PASI-75 response[a]	285 per 1000	487 per 1000 (95% CI: 353 to 669)	RR 1.71 (1.24 to 2.35)	278 (2 RCTs)	Low[b]
Treatment-related adverse events requiring withdrawal[c]	35 per 1000	34 per 1000 (95% CI: 12 to 29)	RR 0.96 (0.35 to 2.64)	404 (2 RCTs)	Low[d]

Abbreviations: CI, confidence interval; PASI-75, Response to therapy has achieved a 75% or more reduction in the Psoriasis Area and Severity Index score from baseline; RCTs, randomized controlled trials; RR, risk ratio; UVB, ultraviolet B light.

[a]PASI-75 response (number of participants with event) 6 to 8 weeks after start of treatment. The risk with standard therapy is based on the mean number of events across the control groups. Calculation regarding PASI-75 response concerning Brockow 2007a and Brockow 2007b: Number of events: 22 + 14 = 36, total number of participants: 66 + 60 = 126, risk per 1000:36/126 * 1000 = 285. We downgraded the certainty of evidence by one level for this outcome. One level because of study limitations (risk of bias). Random sequence generation and allocation concealment were judged low risk of bias but blinding of participants and personnel as well as outcome assessment were judged as high risk of bias. Incomplete outcome data, selective outcome reporting, and other bias were judged as unclear risk of bias.

[b]We downgraded the certainty of evidence by two levels for this outcome. We downgraded one level because of study limitations (risk of bias). Due to lack of blinding, we judged a high bias of performance bias. We downgraded one level because of high probability of publication bias. A large number of studies included in the review did not contribute to the outcome. Both studies were conducted by the same sponsor.

[c]Treatment-related adverse events requiring withdrawal (number of participants withdrawing) 3 to 8 weeks after the start of treatment. The risk with standard therapy is based on the mean number of events across the control groups. Calculation regarding PASI-75 response concerning Klein 2011 and Leaute-Labreze 2001: Number of events: 2 + 7 + 0 = 9, total number of participants: 58 + 179 + 21 = 258, risk per 1000:9 / 258 * 1000 = 35. We downgraded the certainty of evidence by one level for this outcome. One level because of study limitations (risk of bias). Random sequence generation and allocation concealment were judged low risk of bias but blinding of participants and personnel as well as outcome assessment were judged as high risk of bias. Incomplete outcome data, selective outcome reporting, and other bias were judged as unclear risk of bias.

[d]We downgraded the certainty of evidence by two levels for this outcome. We downgraded one level because of study limitations (risk of bias). Due to lack of blinding, we judged a high bias of performance bias. We downgraded one level because of high probability of publication bias. A large number of studies included in the review did not contribute to the outcome.

3.4 | Assessment of risk of bias and quality of evidence

We provide a summary of the risk of bias assessment of the six included studies in Table 3. We judged a high risk of bias for two items of one[17] and for one item of the other[16] of the two studies included in the meta-analyses on PASI-75 response. We also judged a high risk of bias for two items of one[20] and for one item of the other[21] of the two studies included in the meta-analyses on treatment-related adverse events requiring withdrawal.

4 | DISCUSSION

4.1 | Overall completeness and applicability of evidence

Seven of the eight included studies were published 2007 or earlier, and we can assume that the majority of patients were treated 10 to 20 years ago. Nonetheless, we presume that the principle treatment procedures might not deviate considerably from the current practice. The primary beneficial outcome PASI-75 was reported in two out of eight included studies.[16,17] The primary adverse outcome treatment-related adverse events requiring withdrawal was reported in two other between-participant studies.[20,21] None of the predefined secondary outcomes were reported, so there were no patient-reported outcomes. Ultraviolet B phototherapy might pose a risk of carcinogenesis, especially of squamous cell carcinoma, and thus the cumulative exposure time should be controlled.[24,25] The studies included in the present review lack long-term observation and secondary neoplasia was not addressed. The majority of studies were conducted by non-academic institutions with exposure to commercial interests. Therefore, a financial conflict of interest might be present in most if not all of the included studies. Five of the eight studies were conducted in Germany. Key issue is that most included studies did not contribute primary outcome data. Furthermore, the primary beneficial outcome data were reported by two small unblinded trials conducted by a single group of investigators. There was no information for the outcomes on salt water baths + UVB vs no UVB.

4.2 | Quality of the evidence

We downgraded the certainty of evidence of the primary beneficial outcome PASI-75 by two levels (low quality of evidence).[16,17] The concerning two trials were conducted by the same group, and one of the two trials was funded by the German Spas Association. Likewise, we downgraded the certainty of evidence of the primary adverse outcome treatment-related adverse events requiring withdrawal by two levels (low quality of evidence).[20,21] With regard to both outcomes,

TABLE 5 Characteristics of study design, participants, interventions, and outcome assessment

Study (comparison)	Design, setting	Participants (I/C)	Test intervention	Control intervention	Review outcomes
Schiener 2007 (#1)[a]	Parallel group[b], 4 groups, 102 centers DE, outpatient	N randomized 310/321. N analyzed 299/305, mean age 46/47, males 57.5%/65.2%.	SW bath (250 g NaCl dissolved in 1 L TW) + UVB (NB, BB, selective)	Bath PUVA (0.5 mg methoxsalen dissolved in 1 L TW + UVA)	Predefined: None
Arnold 2001 (#2)[c]	Parallel group[b], 2 groups, 1 center NL, outpatient	N randomized 20/20, mean age 41/49. N analyzed 16/17.	SW bath (6.7 g NaCl dissolved in 1 L TW) + UVB (NB)	Psoralen bath (5.7 mg methoxsalen dissolved in 1 L TW) + UVB (NB)	Predefined: None
Brockow 2007a (#2)[c] high saline	Parallel group[b], 2 groups, 4 centers DE, outpatient	N randomized 81/79, mean age 47.5/49.0, males 59%/62%. N analyzed 79/71.	SW bath (250 to 270 g NaCL measured in 1 L natural spring water) + UVB (NB, BB, or selective)	UVB only (NB, BB, selective)	Predefined primary outcome: PASI-75 at 6 weeks
Brockow 2007b (#2)[c] low saline	Parallel group[b], 2 groups, 5 centers DE, outpatient	N randomized 81/83, mean age 49.8/50.0, males 74%/57%. N analyzed 79/64.	SW bath (45 to 120 g NaCL measured in 1 L natural spring water) + UVB (BB or selective)	UVB only (BB, selective)	Predefined primary outcome: PASI-75 at 6 weeks
Dawe 2005 (#2)[c]	Paired body parts[d], 1 center UK, unclear if outpatient	Arms or legs: N randomized 60, mean age 38, males 45%. N analyzed 58.	SW bath (150 g commercial Dead Sea salt dissolved in 1 L TW) + UVB (NB)	UVB only (NB)	Predefined primary outcome: TRAERW at 8 weeks
Gambichler 2001 (#2)[c]	Paired body parts[d], 1 center DE, outpatient	Elbows: N randomized 10, mean age 36, males 40%. N analyzed 10.	SW bath (240 g NaCl dissolved in 1 L TW) + UVB (BB)	TW bath + UVB (BB)	Predefined: None
Klein 2011 (#2)[c]	Parallel group[b], 2 groups, 30 centers DE, outpatient	N randomized 183/184. N analyzed 179/177, mean age 45.0/45.8, males 56.0%/60.5%.	SW bath (100 g commercial Dead Sea salt dissolved in 1 L TW) + UVB (NB)	UVB only (NB)	Predefined primary outcome: TRAERW at 8 weeks
Leaute-Labreze 2001 (#2)[c]	Parallel group[b], 3 groups, 1 center FR, outpatient	N randomized 24/21, mean age 44.5/48.5. N analyzed 24/21.	SW bath (250 g NaCl measured in 1 L natural spring water) + UVB (NB)	UVB only (NB)	Predefined primary outcome: TRAERW at 3 weeks
Schiener 2007 (#2)[c]	Parallel group[b], 4 groups, 102 centers DE, outpatient	N randomized 310/301. N analyzed 299/285, mean age 46/47, males 57.5%/57.0%.	SW bath (250 g NaCl dissolved in 1 L TW) + UVB (NB, BB, selective)	TW bath + UVB (NB, BB, selective)	Predefined: None
Schiener 2007 (#2)[c]	Parallel group[b], 4 groups, 102 centers DE, outpatient	N randomized 310/301. N analyzed 299/270, mean age 46/47, males 57.5%/58.5%.	SW bath (250 g NaCl dissolved in 1 L TW) + UVB (NB, BB, selective)	UVB only (NB, BB, selective)	Predefined: None

Abbreviations: BB, broad-band UVB (280 to 320 nm); DE, Germany; FR, France; I/C, intervention vs comparator; N, number of participants/body parts; NB, narrow-band UVB (311 nm); NL, Netherlands; PASI-75, Response to therapy assessed by the percentage of people or limbs who have achieved a 75% or more reduction in their Psoriasis Area and Severity Index (PASI) score from baseline; PUVA, psoralen (methoxsalen) bath + UVA; selective, selective UVB (300 to 320 nm); SW, salt water; TRAERW, Treatment-related adverse events requiring withdrawal; TW, tap water; UVA, ultraviolet A light (320 to 400 nm); UVB, ultraviolet B light.

[a]Comparison #1: Salt water bath plus UVB vs other treatment without UVB.

[b]Parallel group: The parallel group design creates between-participant data. The participants are individually randomized to one of two (or more) intervention groups, and a single measurement for each outcome (and each comparison) from each participant is collected and analyzed.

[c]Comparison #2: Salt water bath plus UVB vs other treatment plus UVB or UVB only.

[d]Paired body parts: The paired comparison creates within-participant data. Paired refers to a body part that is present on both sides of the body. We considered multiple observations for the same outcome, specifically, multiple body parts receive different interventions, such as comparisons of right vs left arm.

we downgraded one level because of study limitations (risk of bias). Due to lack of blinding, we judged a high bias of performance bias. We downgraded one additional level because of high probability of publication bias.

A large number of studies included in the review did not contribute to the outcome. In general, the reporting did not facilitate a clear and instant understanding. The variety in outcome reporting reduced the potential of pooling homogeneous data considerably. Many data were

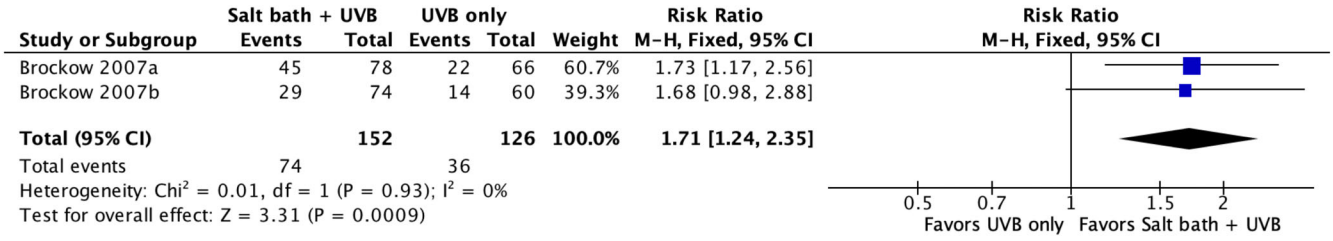

FIGURE 2 Forest plot of comparison Salt bath + UVB vs UVB alone, outcome: PASI-75. CI, confidence interval; Fixed, fixed effect analysis model; M-H, Mantel-Haenszel analysis method; UVB, ultraviolet B-light

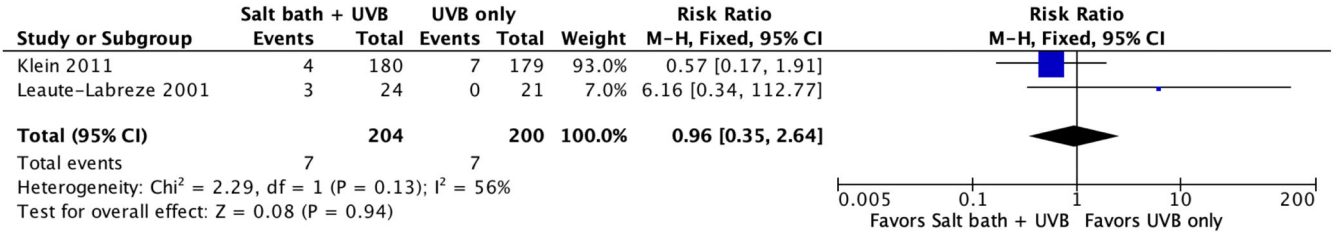

FIGURE 3 Forest plot of comparison Salt bath + UVB vs UVB alone, outcome: Treatment-related adverse events requiring withdrawal. CI, confidence interval; Fixed, fixed effect analysis model; M-H, Mantel-Haenszel analysis method; UVB, ultraviolet B-light

not eligible for meta-analysis, which may create a selection bias within the review. The authors of four studies[15,18,19,21] did not report a participant flow diagram. Acknowledging the study limitations in the reporting of the two primary outcomes, we judge an unclear internal validity. Secondary outcomes of these review were not measured by any of the included studies; therefore, we were unable to determine the certainty of evidence for these outcomes. It should be acknowledged that some studies tried to blind outcome assessment and assessed if the blinding could be realized. In general, lack of blinding of outcome assessment contributed to a high risk of bias in most studies.

4.3 | Agreements and disagreements with other studies or reviews

The Ontario Health Technology Assessment[26] included four RCTs in a systematic review that are also included in the present review.[16,17,21,22] The authors concluded that "Spa salt water baths prior to phototherapy did increase short term clinical response of moderate-to-severe plaque psoriasis", and judged a high quality and adequate study evidence for this statement. The Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA), the highest decision-making body concerning the distribution of the Statutory Health Insurance funds in Germany commissioned the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) to evaluate balneophototherapy in psoriasis.[27] Two of the four included studies are not publicly available, and the rest of two studies are included in the present review. IQWiG did not publish any update as of April 2020. The G-BA decided that indoor salt-water baths followed by artificial ultraviolet B-light for patients with moderate-to-severe chronic plaque psoriasis could be reimbursed not only when done in hospitals but also in practices.[28] Consequently, the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung, KBV) in Germany reported that, as of December 31, 2013, 827 physicians in practice were licensed to offer this intervention and claim reimbursement.[29] In a Cochrane Review, Chen 2013[30] did not detect a difference in the effect between various types of phototherapy, which may support our proceeding to not differentiate the concerning subtypes. In contrast, Almutawa 2013[31] concluded in another systematic review on ultraviolet based therapy for psoriasis, quote: "As a monotherapy, PUVA was more effective than NB-UVB, and NB-UVB was more effective than BB-UVB and bath PUVA in the treatment of adults with moderate to severe plaque-type psoriasis, based on clearance as an end point."

4.4 | Adverse events

We did not search specifically for adverse events, instead we selectively described some adverse events identified in the included studies. Six studies reported various adverse events observed with the assessed people in the salt bath + UVB group as well as with those in the UVB alone group, for example, dermatitis solaris, phototoxic reaction, burning, itching, stinging, itchy papular eruption. Together, there was no significant difference between groups.

4.5 | Outlook

We recommend further RCTs that assess PASI-75, with detailed reporting of the outcome, as well as treatment-related adverse

events requiring withdrawal. Future studies should be independently funded and should ensure blinding of assessment and should enable blinding of performance. The time points of assessing any outcome should be specified. We think that "end of treatment" might not be sufficiently clear. Several time points should be used to allow matching with other studies. The number of people or limbs available for analysis should be given for every time point. The included studies lacked data on all secondary outcomes. These outcomes should be considered in future studies. The limited number of trials and centres suggest a need for increased generalisability in the evidence base for this treatment. Future studies should consider potential harm by UVB exposure. Thus, it is important to keep contact with patients, general practitioners, and dermatologists and inform about the well-being of the participants on a regular basis. In this context it seems meaningful to develop core outcomes for psoriasis treatment trials through the Cochrane Skin Core Outcome Set Initiative (CS-COUSIN; http://cs-cousin.org). To consider any potential harm by UVB exposure, future study protocols should include long-term observations. Future studies should clarify the reporting according to the CONSORT statement.[32]

5 | CONCLUSIONS

With respect to PASI-75, primary beneficial outcome, low-certainty evidence in two studies indicates that people with chronic plaque psoriasis may see a greater reduction in psoriasis severity after treatment with indoor salt bath + UVB compared against UVB alone. Low-certainty evidence for the same comparison in two other studies indicates that people with chronic plaque psoriasis may experience little to no difference in risk of treatment-related adverse events requiring withdrawal. Therefore, we cannot draw clear conclusions regarding the benefit or harm of indoor (artificial) salt water baths followed by exposure to artificial UVB for treating chronic plaque psoriasis in adults.

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CONFLICT OF INTEREST

Marco Harari: "Besides my work as a researcher at the Dead Sea and Arava Science Centre, I am the medical director at the DMZ Medical Centre, which provides Dead Sea climatotherapy." Thilo Gambichler: "Since 1998, I have been performing research in the field of indoor salt water baths followed by artificial ultraviolet B light. I am an author of the following studies Gambichler 2001 (included study) and Gambichler 2000b (excluded study)."

AUTHOR CONTRIBUTIONS

Frank Peinemann was the contact person with the editorial base. Frank Peinemann coordinated contributions from the coauthors and wrote the final draft of the review. Frank Peinemann, Marco Harari, Sandra Peternel, Thalia Chan, Thilo Gambichle screened papers against eligibility criteria. Frank Peinemann obtained data on ongoing and unpublished studies. Frank Peinemann, Marco Harari, Sandra Peternel, Thilo Gambichle appraised the quality of papers. Frank Peinemann, Marco Harari, Sandra Peternel, Thalia Chan, Thilo Gambichle extracted data for the review and sought additional information about papers. Frank Peinemann entered data into RevMan. Frank Peinemann, Marco Harari, Sandra Peternel, Thilo Gambichle analyzed and interpreted data. Frank Peinemann, Marco Harari, Sandra Peternel, Alexander M. Labeit, Thilo Gambichle worked on the methods sections. Frank Peinemann, Marco Harari, Sandra Peternel, Thilo Gambichle drafted the clinical sections of the background and responded to the clinical comments of the referees. Frank Peinemann, Marco Harari, Sandra Peternel, Alexander M. Labeit, Thilo Gambichle responded to the methodology and statistics comments of the referees. David Chan checked the Plain language summary section. Frank Peinemann is the guarantor of the update.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Cochrane Database of Systematic Reviews at https://doi.org/10.1002/14651858.CD011941.pub2.

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