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Balneotherapy (or spa therapy) for rheumatoid arthritis. An abridged version of Cochrane Systematic Review

Arianne P Verhagen[1], Sita MA Bierma-Zeinstra[1], Maarten Boers[2], Jefferson R Cardoso[3], Johan Lambeck[4], Rob de Bie[5], Henrica CW de Vet[6]

[1]Department of General Practice, Erasmus Medical Center, Rotterdam, The Netherlands
[2]Department of Clinical Epidemiology, VU University Medical Center, Amsterdam, Netherlands
[3]Laboratory of Biomechanics and Clinical Epidemiology, PAIFIT Research Group, Universidade Estadual de Londrina, Londrina, Brazil
[4]Faculty of Kinesiology and rehabilitation sciences, Katholieke Universiteit Leuven Tervuursevest, Leuven, Belgium
[5]Department of Epidemiology, Maastricht University, Maastricht, The Netherlands
[6]Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands

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Correspondence: Arianne P Verhagen, Dept General Practice, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: a.verhagen@erasmusmc.nl

Abstract

Background. Treatment options for rheumatoid arthritis (RA) include pharmacological interventions, physical therapy treatments and balneotherapy.

Aim.To evaluate the benefits and harms of balneotherapy in patients with RA.

Design.A systematic review

Population. Studies were eligible if they were randomised controlled trials consisting of participants with definitive or classical RA.

Methods. We searched various databases up to December 2014.Balneotherapy had to be the intervention under study, and had to be compared with another intervention or with no intervention. We considered pain, improvement, disability, tender joints, swollen joints and adverse events among the main outcome measures. We excluded studies when only laboratory variables were reported as outcome measures.Two review authors independently selected trials, performed data extraction and assessed risk of bias.

Results. This review includes nine studies involving 579 participants. Most studies showed an unclear risk of bias in most domains.

We found no statistically significant differences on pain or improvementbetween mudpacks versus placebo (1 study; n=45; hand RA; very low level of evidence).Concerning the effectiveness of additional radon in carbon dioxide baths, we found no statistically significant differences between groups for all outcomes at three-month follow-up (2 studies;n=194; low to moderate level of evidence). We noted some benefit of additional radon at six months in pain (moderate level of evidence). One study (n=148) compared balneotherapy (seated immersion) versus hydrotherapy (exercises in water), land exercises or relaxation therapy. We found no statistically significant differences in pain or in physical disability (very low level of evidence) between groups. We found no statistically significant differences in pain intensity at eight weeks, but some benefit of mineral baths in overall improvement at eight weekscompared toCyclosporin A (1 study; n=57; low level of evidence).

Conclusion.Overall evidence is insufficient to show that balneotherapy is more effective than no treatment; that one type of bath is more effective than another or that one type of bath is more effective than exercise or relaxation therapy.

Clinical rehabilitation impact. We were not able to assess any clinical relevant impact of balneotherapy over placebo, no treatment or other treatments.

Background

Rheumatoid arthritis (RA) is an autoimmune disease characterised by chronic inflammation of the peripheral joints. In adults, the incidence of new cases is 50/100 000/y and one-year prevalence is between 500 and 600/100 000 (0.5% to 1.0%).[1] Common symptoms of RA consist of a combination of pain, fatigue, stiffness, reduced range of motion in the joints and muscle weakness. Inflammation can cause progressive destruction of articular and periarticular structures.[2, 3] RA can affect all joints in the body. The natural course of the disease is a slow but inexorable deterioration in physical condition, leading to difficulty in activities of daily living and poor quality of life. Rheumatoid arthritis is a multi-system disease that can affect internal organs, causing premature death. With adequate treatment targeted towards strongly reducing or abolishing inflammatory disease, many of these consequences can be prevented.

The term 'balneotherapy' comes from the Latin 'balneum' (bath). The term is classically used in (Eastern) European countries when natural mineral or thermal waters are used for bathing, drinking and inhalation. Recently a position paper was published with a proposal for, amongst others, a definition of balneotherapy.[4] One of the core elements of balneotherapy is the use of (natural) mineral waters, gases and peloids (including packs = local application of peloids), often in health resorts (spas). In most European countries, balneotherapy often takes place at centres with thermal baths or seawater baths.[4] In Israel, the main health resort area is located along the western shore of the Dead Sea. The unique environmental conditions in this area are considered beneficial for patients suffering from rheumatic disease.[5]

In Homeric times, baths were applied primarily to cleanse and refresh. At the time of Hippocrates, bathing was regarded as more than a simple hygienic measure. It was considered beneficial in curing most illnesses.[6] The Romans used water for treatment of orthopaedic conditions, but after the Roman era, spa therapy fell into disuse. In the sixteenth century, baths were rediscovered. Since that time, spa therapy has been practised continuously in the management of musculoskeletal conditions.[6-9]

Balneotherapy is prescribed most often for patients with any form of arthritis, including fibromyalgia. Positive effects have been mentioned in the treatment of psoriasis as well.[10]

Exercise in warm (tap) water is usually called 'hydrotherapy' or 'aquatic therapy'. This Cochrane review focuses on balneotherapy only, which consists of bathing in natural mineral or thermal waters, using mudpacks or doing both.

The mechanism by which balneotherapy might work is not clear. Water (thermal water, sea water) is generally used at a temperature of between 34 °C and 36 °C.[4, 11] Hydrostatic force (Archimedes' principle) brings about relative pain relief by reducing loading;[11] water reduces gravity in painful and rheumatic joints. The warmth and buoyancy of water may block nociception by acting on thermal

receptors and mechanoreceptors.[12] Warm water may also enhance blood flow, which is thought to help in dissipating algogenic chemicals, and may facilitate muscle relaxation.[13] Apart from these mechanical and thermal mechanisms, one should not undervalue the psychological mechanisms of the spa environment. The related mental relaxation may also play a role in pain relief.[7]

The aim of balneotherapy is to improve the range of joint motion, relieve muscle spasm, maintain or improve functional mobility, soothe pain and, as a consequence, relieve patients' suffering and help them feel well.[4, 5, 14, 15]

No cure for RA is known at present, so treatment often focuses on management of symptoms such as pain, stiffness and mobility. Treatment options include pharmacological interventions,[16-25] physical therapy [26, 27] and balneotherapy.[8] Since our last publication of this Cochrane review,[8] several systematic reviews and meta-analyses on the effectiveness of balneotherapy have been published.[13, 28, 29] These reviews either combine balneotherapy and hydrotherapy [13, 29] or combine different diseases.[28] Despite its popularity, reported scientific evidence on the effectiveness or efficacy of balneotherapy is sparse. This review evaluates the benefits and harms of balneotherapy in patients with rheumatoid arthritis (RA) in terms of pain, improvement, disability, tender joints, swollen joints and adverse events.

Methods

Selection criteria

Studies were eligible if they were randomised controlled trials (RCTs).Participants had rheumatoid arthritis (RA), with definitive or classical RA as defined by the American Rheumatism Association (ARA) criteria of 1958,[30] the ARA/American College of Rheumatology (ACR) criteria of 1988 [31] or the ACR/EUropean League Against Rheumatism (EULAR) criteria of 2010,[32] or by studies using the criteria of Steinbrocker.[33]

Balneotherapy had to be the intervention under study, and had to be compared with another intervention or with no intervention. Balneotherapy is defined as bathing in natural mineral or thermal waters (*e.g.* mineral baths, sulphur baths, Dead Sea baths), using mudpacks or doing both.The World Health Organization (WHO) and the International League Against Rheumatism (ILAR) determined in 1992 a core set of eight endpoints for clinical trials concerning patients with RA.[34] Major outcomes that we will consider are pain, improvement, disability, tender joints, swollen joints, withdrawals due to adverse events and serious adverse events.Other outcomes that we considered include patient global assessment, physician global assessment, stiffness, range of motion, activities of daily living, quality of life, morning stiffness, walk time, hand grip strength and Ritchie index.

Search strategy

We searched the Cochrane 'Rehabilitation and Related Therapies' Field Register (to December 2014), the Cochrane Central Register of Controlled Trials (2013, Issue 1), MEDLIINE (1950 to December 2014), EMBASE (1988 to December 2014), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to December 2014), the Allied and Complementary Medicine Database (AMED) (1985 to December 2014), PsycINFO (1806 to December 2014) and the Physiotherapy Evidence Database (PEDro) (to December 2014). We applied no language restrictions, but studies not reported in English, Dutch, Danish, Swedish, Norwegian, German or French are awaiting assessment.We also searched the WHO International Clinical Trials Registry Platform for ongoing and recently completed trials.In MEDLINE, the subject-specific strategy was combined with the sensitivity- and precision-maximising version of the Cochrane Highly Sensitive Search Strategy [35] used to identify randomised trials in MEDLINE and modified for use in other databases.
We also searched the reference lists of articles and contacted experts in the field.

Data collection and analysis

Selection of studies. Initially, two review authors (SMAB-Z, JL) independently selected trials by inspecting titles, keywords and abstracts to determine whether studies met the inclusion criteria regarding design, participants and interventions. We retrieved for final assessment full publications of studies of any possible relevance. Next, we used a standardised form to independently perform the final selection of trials to be included in the review. We resolved disagreements by consensus and, if necessary, by third party adjudication (APV).

Data extraction and management. Two review authors (JRC, JL) independently extracted data on trial methods, participants, interventions, types of outcome measures, duration of follow-up, loss to follow-up and results using a standardised data extraction form. We resolved disagreements by consensus and, if necessary, by third party adjudication (APV).

Assessment of risk of bias in included studies. Two review authors (RAdB, HCWdV) independently assessed risk of bias by using the assessment tool developed by The Cochrane Collaboration.[35] This tool involves assessment of randomisation (sequence generation and allocation concealment), blinding (of participants, care providers and outcome assessors), completeness of outcome data, selection of outcomes reported and other sources of bias (baseline comparability, co-interventions, compliance, timing of outcome measures). All items could be scored as having high, low or unclear risk of bias. We resolved disagreements by consensus; if disagreement persisted, a third review author (APV) made a final decision.

*Measures of treatment effect.*We presented various outcome measures separately. For dichotomous data, we expressed results, if possible, as risk ratios (RRs) with corresponding 95% confidence

intervals (CIs). We calculated mean differences (MDs) or, when scales for outcome measures were dissimilar, standardised mean differences (SMDs) with 95% confidence intervals for continuous data.[36]

Treatment allocation was done at an individual level in all trials, and no cluster-randomised or cross-over trials were found, so the unit of analysis was the individual participant.

When possible, we contacted trial authors to request missing data, and we performed intention-to-treat analyses to include all randomly assigned participants. For dichotomous data, we performed a worst-case scenario when all missing people in the intervention group had a bad outcome, although none of the missing people in the control group had such an outcome. However for continuous data, when dropouts were identified, we used the actual number of participants contributing data at the relevant outcome assessment. Unless missing standard deviations could be derived from confidence intervals or standard errors (from the same study), we did not assume values for the purpose of presenting them in the analyses.

We assessed heterogeneity between pooled trials by using a combination of visual inspection of graphs and consideration of the I^2 statistic.[37] Substantial heterogeneity is defined as I^2 greater than 50%.

Available data are insufficient for assessment of publication bias via a prepared funnel plot, so publication bias cannot be assessed.

Data synthesis. We used RevMan Analyses (RevMan5) to analyse the data. In the previous review,[8] review authors did not pool data because the included trials were considered clinically heterogeneous in terms of study populations and interventions. Should pooling be possible with new trials included, we will pool results of comparable groups of trials by using a random-effects model and 95% confidence intervals.

Preplanned stratified analyses included: 1) trials comparing balneotherapy versus no treatment or waiting list controls; 2) trials comparing different types of balneotherapy; and 3) trials comparing balneotherapy versus other treatment(s) (*e.g.* exercise, oral medication).

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system was used to evaluate the overall quality of evidence.[38] The quality of the evidence was based upon five domains and was downgraded by one level for each of these factors when encountered: 1) limitations in design, 2) indirectness of evidence (*i.e.*, generalisability of findings), 3) unexplained heterogeneity or inconsistency of results (significant statistical heterogeneity (I^2>50%) or inconsistent findings among studies, 4) imprecision (total number of participants <300 for each outcome) and 5) high probability of publication bias. Two review authors (SMSB-Z,APV) determined these factors. We considered single randomised studies (N.<300 for dichotomous outcomes and N.<400 for continuous outcomes) to be inconsistent and imprecise and to provide "low-quality evidence", which could be

further downgraded to "very low-quality evidence" for limitations in design (*i.e.,* high risk of bias), indirectness or other considerations. We applied the following levels of quality of evidence.

- High quality: Further research is very unlikely to change the level of evidence. Data are sufficient and have narrow confidence intervals. No reporting biases are known or suspected; all domains were fulfilled.
- Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; one of the domains was not fulfilled.
- Low quality:Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; two of the domains were not fulfilled.
- Very low quality: Great uncertainty surrounds the estimate; three of the domains were not fulfilled.

Results

Description of studies

*Search results.*A search conducted for this update resulted in 210 references, from which two review authors (JL, APV) independently selected 16 additional references on the basis of title and abstract. Of these, two studies were found to be eligible on the basis of full paper assessment and were included in this review (see Figure 1).[39, 40] Final selection based on consensus resulted in inclusion of nine studies in this review, of which five were of Israeli origin, although they were written in English.[39, 41-44]

Participants. A total of 579 participants were enrolled, and the number of participants in the intervention groups ranged from eight to 67 (see Table I). In six of the nine studies, the smallest study arm included fewer than 30 participants, meaning that most studies were underpowered. In seven studies, researchers used ARA criteria when selecting participants, and in two studies, they used the Steinbrocker criteria.[45, 46] All studies included participants with RA as defined by ARA or Steinbrocker criteria, although the severity of RA differed slightly between studies. When mentioned, the percentage of males was between 5% and 40%, and mean age ranged from 39 to 62.4 years.

Interventions. Six studies had two treatment arms, and the other three studies had four treatment arms. Only once was a placebo control used in comparison with mudpacks.[39] In two studies, a no-treatment control group was used.[43, 44] In both studies, participants were aware of the fact that they did not receive baths as treatment. In one other study, the drug treatment group was the control group.[46] In all but one study,[45] the intervention included mineral baths, and in one study, the intervention was given in combination with mudpacks.[41] Two studies evaluated Dead Sea baths,[42, 44] and two studies evaluated the added value of radon over carbon dioxide in the bath.[40, 47]

In all studies, the baths were prepared at between 35 °C and 38 °C. All participants continued their medication during balneotherapy. One study mentioned standardised exercise therapy,[45] and in another study, relaxation exercises were allowed.[46] All studies but one were performed at spa resorts; only Codish [39] provided mudpacks (and placebo mudpacks) to be used at home.

Outcome measures. All studies used several outcome measures including pain and function. Often a standard set of outcome measures was used, such as duration of morning stiffness, 15-meter walk time, hand grip strength, Ritchie index, severity of disease as assessed by participant or physician and laboratory variables. In two studies,[45, 47] investigators used a 'quality of life' instrument (Arthritis Impact Measurement Scales (AIMS or AIMS2). Three studies [39, 46, 47] reported response to treatment or improvement, but investigators in different studies defined it differently (see Table I). The overall follow-up period was three months; only two studies reported six-month follow-up.[40, 47]

Risk of bias in included studies. Four studies described their randomisation procedure; three of these studies were considered to use a concealed randomisation procedure (Figures 2 and 3).[40, 45, 47] Blinding of the observer/outcome assessor is mentioned in all studies, but in several studies, the participant reported the main outcome, and it was unclear whether the participant was blinded, which means that we scored blinding of the outcome assessor as unclear (unclear risk of bias).[43-46] Four studies mentioned blinding of the caregiver,[39, 40, 42, 47] but the success of blinding was never evaluated.

Two studies were scored as having low risk of bias on 'other biases' because study authors clearly mentioned that groups were comparable at baseline, co-interventions were comparable and compliance was acceptable.[40, 47] Only three studies were considered to have no limitations in design, meaning a low risk of bias in most domains.[40, 42, 47] In terms of the risk of bias assessment, the Kappa between two review authors appeared to be moderate at 0.68.

Effects of interventions

Data presented in the papers, even after communication with the study authors, were too scarce to enable 'between-group' analysis in almost half the studies. Also the studies used different interventions or comparison treatments and a wide variety of outcome measures; therefore interventions and outcome measures were considered heterogeneous.

One study assessed harms of balneotherapy;[46] only one participant complained of headache. In this study, most side effects were found in the control group (Cyclosporin A); between 4% and 16% of participants experienced various side effects such as gastrointestinal disturbance (one participant; 4%) and nephrotoxicity (four participants; 16%).[46]

1) Trials comparing balneotherapy versus placebo or no treatment/waiting list controls

One study (N.=45) compared mudpacks *versus* placebo mudpacks for hand RA.[39]

We found no statistically significant differences between groups in terms of pain intensity (MD 0.50, 95% CI -0.84 to 1.84; absolute difference 0.5%), improvement (or 'response rate') (RR 0.96, 95% CI 0.54 to 1.70; absolute difference -2%) and number of tender joints (MD -4.60, 95% CI -8.72 to -0.48; absolute difference -16%) (see Table II). Therefore we conclude that very low-level evidence (single study, downgraded by design) showed unclear benefit of mudpacks over placebo in hand RA in terms of pain, response rate and number of tender joints. Physical disability was not reported. Also no data were presented on improvement, withdrawals due to adverse events or serious adverse events.

Two studies (N.=76) included a control group receiving no treatment.[43, 44] Both studies suffer from high risk of bias and low power; short-term improvement was mentioned in all treatment groups compared with control groups for most outcome measures (see Table I). No data were provided on pain, improvement, physical disability, number of tender and swollen joints, withdrawals due to adverse events or serious adverse events. The study authors' conclusion of improvement was based on pre/post analysis. Data on harm or side effects were not reported.

2) Trials comparing different types of balneotherapy

Three studies compared mineral baths versus tapwater baths.[40, 41, 47] We were able to pool the data from two studies (N.=194) evaluating the effectiveness of additional radon in carbon dioxide baths.[40, 47]

We found no statistically significant differences post treatment and at three months in pain intensity on a visual analogue scale (VAS), but a statistically significant difference in pain in favour of additional radon at six-month follow-up only, with a difference of 9.6 mm on a 100-mm VAS (95% CI 1.6 to 17.6). Both effect estimates show no clinically relevant differences (>15%) (see Table III).

We found no differences post treatment and at three months in terms of improvement in pain frequency on a 4-point scale (no, sporadic, daily, continuous) or improvement in one or more categories, but a significant difference of 30% in favour of additional radon at six-month follow-up (RR 2.3, 95% CI 1.1 to 4.7) (see Table III).

For all other outcomes (physical disability, tender joints, swollen joints, withdrawals due to adverse events and serious adverse events), no data were provided.

Therefore we conclude that moderate-level evidence (downgraded because of imprecision (low power) shows unclear benefit in terms of pain at end of treatment and at three-month follow-up, but benefit of additional radon in carbon dioxide baths for the treatment of participants with RA at six months, although the clinical relevance of this benefit is small. We found low-level evidence (single study) of unclear benefit for improvement at end of treatment and at three-month follow-up, but benefit of additional radon in carbon dioxide baths in the treatment of patients with RA at six months.

Two studies (N.=76) compared Dead Sea salt baths *versus* normal salt baths [42] or sulphur baths,[44] and another study (N.=30) compared sulphur baths *versus* mudpacks.[43] All three studies did not provide sufficient data on pain, improvement, physical disability, number of tender and swollen joints,

withdrawal due to adverse events and serious adverse events for the analysis. The authors of original studies mentioned short-term improvement in all treatment groups on most outcome measurements, but a more profound effect in the groups receiving mineral baths. All studies were of low power, performed a pre/post analysis and presented only point estimates.

3) Trials comparing balneotherapy versus other treatments (e.g. exercise, oral medication)

In one study (N.=35 in each study arm), 'balneotherapy' (seated immersion) was compared with hydrotherapy (exercise in water), land exercise or relaxation therapy.[45] Here balneotherapy was performed with tapwater at 36 °C.

We found no statistically significant differences in pain (MD 0.05, 95% CI -0.32 to 0.42) and physical disability (MD -0.70, 95% CI -1.50 to 0.10). No data were provided on improvement, tender joints, swollen joints, withdrawal due to adverse events or serious adverse events.

Therefore we conclude that a very low level of evidence (single study) and downgraded because of limitations in design (high risk of bias) shows unclear benefit of tapwater bathing over relaxation, exercise or hydrotherapy.

In another study (N.=57), balneotherapy was compared with drug therapy (Cyclosporin A, 3.5 mg/kg).[46] We found no statistically significant differences in terms of pain (0 to 100 VAS) (MD 8, 95% CI -17.54 to 1.54) or swollen joints (MD 1.50, 95% CI -1.25 to 4.25) (see Table IV). We found a statistically significant benefit of mineral baths in terms of overall improvement at eight weeks of 54% (RR 2.35, 95% CI 1.44 to 3.83) and significant benefit of Cyclosporin A at eight weeks in terms of the number of tender joints (MD 8.9, 95% CI 3.8 to 14) (see Table IV). For all other outcome measures (physical disability, withdrawal due to adverse events and serious adverse events), no data were provided.

Very low-level evidence (single study and downgraded because of limitations in design (high risk of bias) suggests some benefit of mineral baths over Cyclosporin A concerning overall improvement, and of Cyclosporin A over mineral baths in terms of the number of swollen joints.

Discussion

Main results

Concerning pain, number of tender joints, ‘response rate’ or improvement, no statistically significant differences were found between mudpacks for the hand and placebo mudpacks (very low level of evidence) or for bathing with tapwater over relaxation, exercise or hydrotherapy (very low level of evidence). Harms were not reported for these comparisons.

In terms of pain, some benefit has been associated with additional radon in carbon dioxide baths for the treatment of patients with RA, but the clinical relevance of this benefit is small (moderate level of evidence). Regarding all other outcome measures (improvement, disability, tender joints, swollen

joints, withdrawal due to adverse events or serious adverse events), we conclude that the benefit of either form of balneotherapy over another is inconclusive.

For pain, a very low level of evidence of unclear benefit was found, butfor overall improvement, we found some benefit of balneotherapy over drug treatment (very low level of evidence). In this comparison, withdrawals due to adverse events were not reported.

Overall completeness and applicability of evidence

Rheumatoid arthritis (RA) is a chronic, progressive and disabling disease that has great impact on quality of life. When balneotherapy is evaluated, the outcome measures used and the follow-up period chosen should be adequate. The main aims of balneotherapy are to maintain or improve functional mobility, soothe pain and let patients feel well. Often a standard set of outcome measures was used. In daily life, patients are trying to deal with pain by using coping strategies. Pain (often assessed by the patient) was reported as an outcome measure in the Methods sections of most studies, but results were seldom reported. A 'quality of life' assessment was reported in only two studies.[45, 47] This is surprising because one of the aims of balneotherapy, or therapy for patients with chronic disease in general, is to improve health-related 'quality of life'. The question can be raised whether the outcome measures used in most studies were specific and responsive enough to enable measurement of treatment effect. Also the follow-up period seems to be rather short. Positive effects of spa therapy have been found in patients with ankylosing spondylitis even after 40 weeks of follow-up.[6]

We noted heterogeneity of the intervention 'balneotherapy'. Once balneotherapy consisted of tapwater, once as mineral baths (38 °C, daily for 20 minutes) + mudpacks (for 20 minutes), twice as radon/carbon dioxide baths (15 times in four weeks, for 20 minutes), twice as Dead Sea baths (daily for 20 to 30 minutes), twice as sulphur baths (daily for 20 minutes), once as a combination of Dead Sea and sulphur baths, once as a combination of sulphur baths + mudpacks (see Table I) and once as only mudpacks. This makes it difficult to determine what the most effective form of balneotherapy is, or even whether an essential element (minerals) in the water is responsible for its effectiveness.

Quality of the evidence

Unfortunately, most studies showed methodological flaws resulting in high risk of bias. Also data presentation was often lacking. When information concerning trial design, especially regarding strategies to avoid bias, is lacking, we could not exclude possible bias in the trial. Therefore, a robust analysis of the effectiveness of balneotherapy cannot be presented.

Potential biases in the review process

Our review might very well suffer from selection bias based on language. We found several studies that were presented in Hebrew, Japanese or one of the Eastern European languages. Often the English

abstract was lacking information about the design of the study. These studies are all awaiting assessment.

We used the criteria of the Cochrane Back Review Group (CBRG) for risk of bias assessment.[48] This tool is a slightly extended version of the one described in the *Cochrane Handbook for Systematic Reviews of Interventions*, although with some sub-items in the different domains, easing the risk of bias assessment. In previous versions of the review, we used the Delphi list, which is comparable with the risk of bias assessment tool of the CBRG.[49] Therefore we observed no major differences concerning risk of bias assessment between the previous version and the current version of the review. Overall this risk of bias assessment tool can be regarded as a reliable and valid instrument.[48, 50] Nevertheless misclassification is always a possibility.

The 'spa environment' is an important factor in treatment results.[5, 51] Many factors may contribute positively to reported effects,[14] such as changes in environment, the 'spa scenery', absence of (house)work duties, physical and mental relaxation, the non-competitive atmosphere with similarly suffering companions, physical therapy and so forth. As such, any benefit of the spa could perhaps be attributed also to the effects of factors unrelated to the "water" therapy *per se*.

Agreements and disagreements with other studies or reviews

The conclusion of this review that evidence is still insufficient to show the effectiveness of balneotherapy is consistent with the conclusion of other reviews.[7, 13, 52] Although the selection criteria differ between reviews, all review authors conclude that poor methodological quality and scarce data presentation make it impossible to draw firm conclusions. The more recent studies are of better methodological rigour, but additional studies are needed.

Authors' conclusions

Implications for practice

Balneotherapy is one of the oldest forms of therapy for patients with arthritis. On pain, we found a low level of evidence of benefit for mineral baths when compared with drug treatment at eight weeks and a moderate level of evidence of benefit of additional radon in carbon dioxide baths for the treatment of patients with RA. Most studies report positive findings but provide insufficient evidence to support their claims. Scientific evidence is insufficient because of high risk of bias in most studies and absence of an adequate statistical analysis.

Implications for research

Large studies with low risk of bias are needed, focusing on appropriate allocation concealment, blinding and adequate data presentation and analysis. The design and reporting of future trials should conform to CONSORT guidelines.

New research should at a minimum use the agreed upon core set of outcome measures for RA supplemented with further specific measures relevant to capture the patient experience, documented to be adequate with the patient responsive to the treatment under study. Follow-up should be of sufficient length to assess long-term effects.

New research should provide full data on outcome measures, including mean and standard deviation or 95% confidence interval.

Future research should examine the effects of balneotherapy not only in pragmatic trials comparing various interventions with each other, but also in more explanatory trials comparing intervention groups versus a no-treatment control group. When possible, the beneficial effect of the 'spa environment' should be considered as a confounder or an effect modifier and accounted for in the design of the trial.

We conclude that performing randomised studies with low risk of bias concerning the effectiveness of balneotherapy is both possible and necessary to provide strong evidence on the effects of balneotherapy.

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Contributions of authors

Arianne P Verhagen (APV) and Henrica CW de Vet (HCWdV) initiated the review; APV wrote the first draft of the review. APV developed the search strategy, and APV and Sita MA Bierma-Zeinstra (SMAB-Z) performed study selection and analysis and wrote the review. Rob A de Bie (RAdB) and HCWdV performed the quality assessment, and Jefferson R Cardoso (JRC) and APV performed data extraction. In this update, Johan Lambeck (JL) helped with the search for and selection of studies. SMAB-Z, RAdB, JRC, Maarten Boers (MB) and HCWdV all critically reviewed successive drafts of the review. APV served as the guarantor of the review.

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Figure 1: Study flow diagram.

Figure 2: Risk of bias graph.

Figure 3: Risk of bias summary.

Table I: Study characteristics.

Table II: Summary of findings: balneotherapy compared with placebo.

Table III: Summary of findings: additional radon in carbon dioxide baths compared with carbon dioxide baths only.

Table IV: Summary of findings: balneotherapy compared with drug treatment.

Table I: Study characteristics.

Study	*Population*	*Interventions*	*Outcome measures*	*Results*
Sukenik 1990a	RA according to ARA criteria; class II and III; N.=30	**I: Dead Sea baths daily**, 35 °C; N.=15 **II: NaCl baths daily;** 35 °C; N.=15 2 weeks intervention; follow-up: 1, 3 months	Morning stiffness (min); 15m walking time (sec); hand grip strength (mm Hg), ADL (6-pt scale); number of active joints, Richie index, patient assessment (11-pt scale)	
Sukenik 1990b	RA according to ARA criteria; class II and III; N.=40	**I: Mudpacks daily**, 42 °C; N.=10 **II: Sulphur baths daily**; 37 °C; N.=10 **III: Mudpacks + Sulphur baths**; N.=10 **IV: No treatment;** N.=10 2 weeks intervention; follow-up: 1, 3 months	Morning stiffness (min); 15m walking time (sec); hand grip strength (mmHg), ADL (6-pt scale); number of active joints, Richie index, patient assessment (11-pt scale)	
Elkayam 1991	RA according to ARA criteria; N.=41	**I: Mineral baths daily + mudpacks**, 38 and 45 °C resp; N.=19 **II: Tapwater baths daily;** 38 °C; N.=22 2 weeks intervention; follow-up: 4, 8, 12 weeks	Morning stiffness (min); 15m walking time (sec); hand grip strength (mmHg), ADL (6-pt scale); number of active joints, Richie index, patient assessment (7-pt scale), physician assessment (7-pt scale)	

Sukenik 1995	RA according to ARA criteria; class II and III; N.=36	**I: Dead Sea baths daily**; N.=9 **II: Sulphur baths daily**; 35 °C; N.=9 **III: Dead Sea + Sulphur baths**; N.=10 **IV: No treatment**; N.=8 12 days intervention; follow-up: 1, 3 months	Morning stiffness (min); 15m walking time (sec); hand grip strength (mmHg), ADL (6-pt scale); number of active joints, Richie index, patient assessment (11-pt scale)	
Hall 1996	Chronic RA according to Steinbrocker criteria class I, II and III; N.=148	**I: Hydrotherapy**; N.=35 **II: Seated emersion**; 36 °C; N.=35 **III: Land exercises**; N.=34 **IV: Progressive relaxation**, N.=35 4 weeks intervention; follow-up: 3 months	Pain (McGill, Beliefs in pain control questionnaire), health status (AIMS-2), morning stiffness (min); 15m walking time (sec); hand grip strength (mmHg), ADL (6-pt scale); number of active joints, Richie index, patient assessment (5-pt scale)	Pain II *vs.* IV: 4 wk: 0.3 (-0.01; 0.61) 3 mo: 0.5 (-0.32; 0.42) Physical activity II *vs.* IV: 4 wk: -0.5 (-1.35; 0.34) 3 mo: -0.7 (-1.5; 0.1)
Yurtkuran 1999	RA according to ACR criteria/Steinbrocker criteria class II and III; N.=57	**I: Balneo therapy**, 35 °C; N.=32 **II: Control group**, CsA disease modifying agent (3.5 mg); N.=25 3 weeks intervention; follow-up: 4, 8 weeks	Pain (VAS), morning stiffness (min); hand grip strength (mmHg), number of active joints, patient assessment (5-pt scale)	Pain: 4 wk: -0.8 (-17.54; 1.54) 8 wk: 9.64 (-1.66; 20.94) Improvement: 8 wk: RR=2.35 (1.44; 3.83)
Franke 2000	Classical or definite RA	**I: Natural spring water (carbon**	Pain intensity (VAS),	Pain intensity:

	according to ACR criteria; N.=60	**dioxide+ radon)**; N.=30 **II: Artificial water (carbon dioxide)**; N.=30 4 weeks intervention; follow-up: 3, 6 months	function (Keitel function index), health status (AIMS); morning stiffness (min) improvement?	1 mo: -2.8 (-15.03; 9.43) 3 mo: -10.8 (-25.18; 3.58) 6 mo: -14.4 (-28.08; -0.72) Improvement: 1 mo: 1.27 (0.69; 2.33) 3 mo: 0.38 (0.64; 2.93) 6 mo: 2.29 (1.1; 4.74)
Codish 2005	RA of hands according to ACR criteria; N.=45	**I: Mineral rich mudpacks**, 30-35 °C; N.=23 **II: Placebo (mineral depleted)**; 30-35 °C; N.=23 3 weeks intervention; follow-up: 1, 3 months	Pain intensity (VAS), 'response rate' number of active joints,	Pain intensity: 1 mo: -0.4 (-1.74; 0.94) 3 mo: 0.5 (-0.84; 1.84) Response rate: 1 mo: 1.05 (0.66; 1.65) 3 mo: 0.96 (0.54; 1.7) Tender joints: 1 mo: -5.1 (-8.58; -1.62) 3 mo: -4.6 (-8.72; -0.45)
Franke 2007	RA according to ACR criteria; N.=134	**I: Natural spring water (carbon dioxide + radon)**; 35 °C; N.=67 **II: Plain water (carbon dioxide)**; 35 °C; N.=67 3 weeks intervention; follow-up: 3, 6 months	Pain intensity (VAS), function (Hanover functional capacity test, Keitel function index), morning stiffness (min), pain medication	Pain intensity: 1 mo: 3.3 (-4.07; 10.67) 3 mo: -1.2 (-10.95; 8.55) 6 mo: -7.1 (-16.93; 2.73)

Table II: Summary of findings: balneotherapy compared with placebo.

Patient or population: participants with rheumatoid arthritis
Settings: unclear
Intervention: balneotherapy (mineral-rich mud compresses)
Comparison: placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk Placebo	**Corresponding risk Balneotherapy**				
Pain intensity VAS, 0-100 (no pain to worst pain ever) Follow-up: 3 months	Mean pain intensity in control groups was **47**	Mean pain intensity in intervention groups was **0.5 higher** (0.84 lower to 1.84 higher)		45 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	MD 0.50 (95% CI -0.84 to 1.84) Absolute difference 0.5% (95% CI -0.84% to 1.84%) Relative percent change 1% (95% CI -2% to 4%) No statistically significant or clinically relevant difference
Improvement Yes/no based on 5 outcome measures (> 30% reduction in number of swollen joints, > 30% reduction in number of tender joints, > 20% improvement in patient VAS for severity of pain and > 20% improvement in physician VAS)	**522 per 1000**	**501 per 1000** (282 to 887)	**RR 0.96** (0.54 to 1.70)	45 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	Absolute difference -2% (95% CI -31% to 27%) Relative percent change 5% (95% CI -42% to 70%) No statistically significant or clinically relevant difference

Follow-up: 3 months **Physical disability** Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Tender joints Number of painful joints Scale from 0 to 28 Follow-up: 3 months	Mean number of tender joints in control groups was **12.5**	Mean number of tender joints in intervention groups was **4.6 lower** (8.7 lower to 0.5 higher)		45 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	Absolute difference -16% (95% CI -31% to 2%) Relative percent change -37% (95% CI -70% to -4%) NNTB 32 (95% CI 10 to 717) MD -4.60 (95% CI -8.72 to -0.48) MD 0.60 (95% CI -0.90 to 2.10)
Swollen joints Number of swollen joints Scale from 0 to 28 Follow-up: 3 months	Mean number of swollen joints in control groups was **1.9**	Mean number of tender joints in intervention groups was **0.6 higher** (0.9 lower to 2.1 higher)		45 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	Absolute difference 2% (95% CI -3% to 8%) Relative percent change 32% (95% CI -47% to 110%) No statistically significant or clinically relevant difference
Withdrawal due to serious adverse events Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Adverse events	See comment	See comment	Not estimable	-	See comment	Not reported

Not reported

*The basis for the assumed risk (*e.g.* median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; NNTB: Number needed to treat for an additional beneficial outcome; RR: Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table III: Summary of findings: additional radon in carbon dioxide baths compared with carbon dioxide baths only.

Patient or population: participants with rheumatoid arthritis
Settings: springs in Bad Brambach, Germany
Intervention: additional radon in carbon dioxide baths
Comparison: carbon dioxide baths only

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Carbon dioxide baths only	Corresponding risk Additional radon in carbon dioxide baths				
Pain intensity VAS, 0-100 mm (no pain to worst pain ever) Follow-up: 3 months	Mean change in pain intensity in control groups was **-4.8 to 4.8**	Mean change in pain intensity in intervention groups was **4.49 lower** (13.41 lower to 4.44 higher)		194 (2 studies)	⊕⊕⊕⊖ **Moderate** [a]	MD -4.49 (95% CI -13.41 to 4.44) Absolute difference 4.5% (95% CI -13.4 to 4.4) No statistically significant or clinically relevant difference
Pain intensity VAS, 0-100 mm (no pain to worst pain ever) Follow-up: 6 months	Mean change in pain intensity in control groups was **0.7 to 7.9**	Mean change in pain intensity in intervention groups was **9.59 lower** (17.57 to 1.7 lower)		194 (2 studies)	⊕⊕⊕⊖ **Moderate** [a]	MD -9.59 (95% CI -17.57 to -1.6) Absolute difference 9.5% (95% CI -17.5 to -1.6) Statistically significant but not clinically relevant difference
Improvement More than 1 category change in pain intensity on 4-point scale (no pain/sporadic/daily/continuous) Follow-up: 3 months	**267 per 1000**	**367 per 1000** (171 to 781)	**RR 1.38** (0.64 to 2.93)	60 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	Absolute difference 10% (95% CI -13% to 33%) Relative percent change

						38% (95% CI -36% to 22%) No statistically significant or clinically relevant difference Absolute difference 30% (95% CI 10% to 60%)
Improvement More than 1 category change in pain intensity on 4-point scale (no pain/sporadic/daily/continuous) Follow-up: 6 months	**233 per 1000**	**533 per 1000**	**RR 2.29** (1.1 to 4.74)	60 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	Relative percent change 129% (95% CI 10% to 474%) Statistically significant and clinical relevant difference
Physical disability Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Tender joints Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Swollen joints Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Withdrawal due to serious adverse events Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Adverse events Not reported	See comment	See comment	Not estimable	-	See comment	Not reported

*The basis for the assumed risk (*e.g.* median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table IV: Summary of findings: balneotherapy compared with drug treatment.

Patient or population: participants with rheumatoid arthritis
Settings: Ataturk Rehabilitation and Balneotherapy Centre, Turkey
Intervention:balneotherapy
Comparison: drug treatment - Cyclosporin A

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Drug treatment - Cyclosporin A	**Corresponding risk** Balneotherapy				
Pain intensity VAS, 0-100 mm (no pain to worst pain ever) Follow-up: 8 weeks	Mean pain intensity in control groups was **18**	Mean pain intensity in intervention groups was **9.64 higher** (1.66 lower to 20.94 higher)		57 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	MD 9.64 (95% CI -1.66 to 20.94) Absolute difference 10% (95% CI -2% to 21%) Relative percent change 53% (95% CI -9% to 116%)
Improvement Global improvement on 5-point scale (very good/good/fair/poor/very poor) Follow-up: 8 weeks	**400 per 1000**	**940 per 1000** (576 to 1000)	**RR 2.35** (1.44 to 3.83)	57 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	No statistically significant or clinically relevant difference Absolute difference 54% (95% CI 33% to 75%) Relative percent change 135% (95% CI 44% to 283%) NNTB 2 (95% CI 2 to 3)

Physical disability Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Tender joints Number of tender joints Scale from 0 to 28 Follow-up: 8 weeks	Mean number of tender joints in control groups was **3.9**	Mean number of tender joints in intervention groups was **8.9 higher** (3.83 higher to 13.97 higher)		57 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	Absolute difference 31% (95% CI 17% to 50%) Relative percent change 228% (95% CI 98% to 358%) NNTB 22 (95% CI 8 to 96) MD 1.50 (95% CI -1.25 to 4.25)
Swollen joints Number of swollen joints Scale from 0 to 28 Follow-up: 8 weeks	Mean number of swollen joints in control groups was **1.9**	Mean number of tender joints in intervention groups was **0.6 higher** (1.25 lower to 4.25 higher)		57 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	Absolute difference 5% (95% CI -4% to 15%) Relative percent change 79% (95% CI -66% to 224%) No statistically significant or clinical relevant difference
Withdrawal due to serious adverse events Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Adverse events Not reported	See comment	See comment	Not estimable	-	See comment	Not reported

*The basis for the assumed risk (*e.g.* median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; NNTB: Number needed to treat for an additional beneficial outcome; RR: Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.