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Original Article

Radon therapy for the treatment of rheumatic diseases—review and meta-analysis of controlled clinical trials

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Abstract
Objective The aim of this study was to analyze the effect of radon therapy on pain in rheumatic diseases.
Methods MEDLINE and MedKur databases were searched for the terms radon plus therapy, rheum, arthritis, and osteo. Radon therapy centers and experts in the field were contacted, proceedings hand-searched, and bibliographies checked for references of potential importance. Included were all prospective randomized controlled clinical trials that compared clinical effects of radon therapy with other interventions in patients with rheumatic diseases and studied pain intensity. Information concerning patients, interventions, results, and methodology were extracted in a standardized manner by all authors independently and summarized descriptively. Reports on pain reduction were pooled for meta-analysis.
Results Five clinical trials with a total of 338 patients and comparing the effect on pain of radon baths (three trials) or radon speleotherapy (two trials) with control intervention in degenerative spinal disease (two trials), rheumatoid arthritis (one trial) and ankylosing spondylitis (two trials) met the inclusion criteria. In meta-analysis, the pooled data showed no difference immediately after treatment (P=0.13) but significantly better pain reduction in the radon group than the control group at 3 months (P=0.02) and 6 months (P=0.002) after treatment.

Conclusions The existing trials suggest a positive effect of radon therapy on pain in rheumatic diseases. With respect to the potential clinical effect and given the increasing public interest in radon therapy, there is an urgent need for further randomized controlled clinical investigations with long-term follow-up.

Keywords Ankylosing spondylitis - Radon - Rheumatoid arthritis - Spa - Spinal disease

Introduction

Radon therapy, namely the exposure to radon for therapeutic purposes, is used for the treatment of rheumatic diseases [1]. A large number of patients are treated in countries with traditions of spa therapy, i.e., central Europe and Russia, but radon therapy is virtually unknown in the U.K., Scandinavia, and the U.S. Despite reports of a potentially increased risk of lung cancer development induced by radon exposure [2, 3], new treatment facilities have been founded in Germany, the Czech Republic, and Hungary in recent years.

For treatment purposes, radon is commonly applied by bathing for about 20 min in water with a radon concentration of 0.3–3 kBq/L or staying for about 1 h in caves or galleries with natural radon concentrations of about 30–160 kBq/m^3. Direct inhalation of vaporized radon water and the drinking of water with a high radon concentration are less common. In eastern European countries, artificially produced radon is frequently used for treatment in so-called aerial baths [4], where the skin is exposed to radon-enriched air in specially designed devices while the patient breathes fresh air.

Radon is taken up by inhalation or transcutaneous resorption, which may be enhanced by concomitant heat or carbon dioxide. Almost all incorporated radon is discharged by exhalation, the remainder being effective in organs and body tissue through radioactive decay and the emission of alpha particles [5].

Animal studies have revealed many changes after radon exposure, including an increase in endorphins and enkephalins in blood [6] and in superoxide dismutase (SOD) activity in liver and kidney [7]. The increase in SOD activity after radon exposure was recently confirmed by Yamaoka et al. [8]. In another study, radon exposure was associated with an increased volume of liposomes and mitochondrial inner membranes of the fascicular zone of the adrenal cortex, suggesting radon-induced neogenesis of the respective membranes [9]. Following serial radon exposure in a radon gallery (total approximately 15 h in 3 weeks), a decrease was found in the stimulated respiratory burst in neutrophils of patients with ankylosing spondylitis [10].

Some authors claim that the clinical benefit may be mediated by radon effects on the skin; and the skin, probably the Langerhans cells, may be the main target organ of radon therapy [11]. In this case, the cutaneous dose would be the most relevant variable for therapy. Activities of radon and radon decay products of about 50 μGy have been demonstrated in the epidermis after immersion in a radon bath of 415 Bq/L [12]. In this regard, the combination of radon and heat may enhance the effects mediated by cutaneous alterations, as radon is discharged with sweat and may cause a significant increase in radon progenies on the skin [13, 14].

Despite these experimental studies showing various changes induced by radon, it must be stated that our understanding of how radon exerts its effects in patients suffering from

rheumatic diseases is very incomplete. Nevertheless, positive clinical reports suggest that this unconventional form of treatment deserves closer attention.

The present meta-analysis was aimed to elucidate whether radon therapy in rheumatic diseases is associated with a significant alleviation of pain, compared to control interventions.

Method

Criteria for considering trials for inclusion

Included were patients suffering from rheumatic disease. The studies had to include at least one treatment group in which radon therapy was applied and reports on pain intensity before and after the intervention.

Search strategy

The MEDLINE database was searched for the terms radon plus therapy/treatment, rheumat, pain, osteoart, joint, and spondyl. The MedKur database of the Balneology and Rehabilitation Sciences Research Institute at Bad Elster (Germany) was also searched using the same terms. Radon therapy centers and experts in the field were contacted, proceedings hand-searched, and bibliographies checked for references of potential relevance.

In a first step, one of the authors (A.F.) selected from the pool of obtained material relating to radon therapy of rheumatic diseases those trials reporting (in title or abstract) on treatments, including uncontrolled case series and experiments. The studies had to include patients with rheumatic diseases treated with radon alone or as an additional therapy and report any clinical outcome. If the study design was not clearly described, the authors were contacted to obtain the missing information. In order to miss no relevant information due to language problems, papers in Russian (most of them without English abstracts) were included rather generously in step 1 if the title suggested a clinical investigation evaluating the effect of radon. More critical analysis was performed later in step 2, when two of the authors (A.F., J.K.) assessed the papers after translation.

All trials selected in step 1 were checked for inclusion criteria by two of the authors (A.F., J.K.) independently (step 2), who finally agreed on trials which met the criteria for inclusion, i.e., were prospective randomized controlled studies in rheumatic disease comparing the effects of radon therapy with those of an intervention without radon exposure and reporting on pain intensity.

To provide better insight into the quality of the papers, we used a modified version of the quality assessment as suggested by Jadad et al. [*15*]: instead of a double-blind study, a blinded observer was sought. This modification was necessary because a double-blind study design is not possible for speleotherapeutic radon exposure.

Summary of selection criteria

Included were all prospective randomized controlled clinical trials that compared clinical effects of radon therapy with another or no intervention in patients suffering from rheumatic disease. Only papers giving all required information and adequately reporting on pain were finally analyzed.

Summary of selected trials

Information on patients, interventions, results, and methodology was extracted in a standardized manner by all authors independently and summarized descriptively.

Meta-analysis for pain reduction

The pain scores were pooled for meta-analysis. In the case of data presentation by median value and 50% range, mean value and standard deviation were estimated. With respect to the heterogeneity of data, a random effect model was applied for calculating the standardized mean difference in pain change (a) after treatment, and (b) 3 months (in Pratzel and coworkers' publications [*11*, *16*] 2 months) and (c) 6 months (in Pratzel and coworkers' publication [*11*, *16*] 4 months) after treatment using the Review Manager software, Version 4.1, of the Cochrane Collaboration [*17*].

Results

Selection process

MEDLINE search produced 88 publications, MedKur search an additional 11. Five more trials were identified by hand-searching, checking bibliographies, and contacting experts on radon therapy. Step 1 produced 27 publications in various languages: 16 in Russian, eight in German, two in English, and one in Dutch (Table 1). These publications were analyzed with regard to the criteria given in step 2, leaving five prospective randomized controlled clinical trials. These five trials were assessed for quality criteria (Table 2).

Table 1 Twenty-seven trials produced by step 1 selection were analyzed with regard to control intervention, randomization, and patient diagnosis. *A* Comparison of radon therapy with another therapy or no therapy. *B* Allocation to groups randomized. *C* Patients likely to have a rheumatic disease. *D* Included only if all three items were answered "yes"

Author, year, reference	A	B	C	D
Zielke et al. 1973 [22]	No	No	Yes	No
Aryppaeva 1974 [23]	No	No	Yes	No
Tsarfis et al. 1974 [24]	No	No	Yes	No
Tsarfis et al. 1975 [25]	No	No	Yes	No
Asalkhanov 1976 [26]	No	No	Yes	No
Fiveiskaia 1976 [27]	No	No	Yes	No
Gerasimenko 1976 [28]	No	No	Yes	No
Pshetakovskii 1976 [29]	No	No	Yes	No
Tsarfis 1976 [30] [a]	No	No	yes	No
Steiner et al. 1979 [31] [b]	Yes	No	Yes	No
Tondii et al. 1979 [32]	No	No	Yes	No
Sorokina et al. 1981 [33] [c]	Yes	No	no	No
Mikunis et al. 1985 [34]	No	No	Yes	No
Trigorieva/Lomsadze 1985 [35]	Yes	No	Yes	No
Tsarfis et al. 1987 [36]	No	No	Yes	No

Author, year, reference	A	B	C	D
Galliamov/Valeev 1990 [37]	No	No	Yes	No
Shliapak et al. 1992 [38]	No	No	Yes	No
Veinpalu et al. 1992 [39]	Yes	No	Yes	No
Bernatzky et al. 1994 [40]	No	No	Yes	No
Lind-Albrecht 1994 [18]	Yes	Yes	Yes	Yes
Pratzel et al. 1993 [16]	Yes	Yes	Yes	Yes
Dicheva et al. 1998 [41]	Yes	No	Yes	No
Falkenbach et al. 1999 [42]	No	No	Yes	No
Pratzel et al. 1999 [11]	Yes	Yes	Yes	Yes
Skorepa et al. 1999 [43]	No	Yes	Yes	No
Franke et al. 2000 [20]	Yes	Yes	Yes	Yes
van Tubergen et al. 2001 [21]	Yes	Yes	Yes	Yes

[a] Only "some of the patients" were reported to have rheumatic disease. Excluded
[b] Crossover design, but no information about allocation. Excluded
[c] Patients had "rheumatic carditis," probably only aftereffects of former rheumatic fever. Excluded

Table 2 Quality assessment of selected trials. *A* Adequate concealment of randomization. *B* Attempt made to blind evaluators. *C* Dropouts described and assessed adequately. *D* Bias due to dropouts or withdrawals taken into account. *E* selected

Author, year, reference	A	B	C	D	E
Lind-Albrecht 1994 [18][a]	Yes	No	No	No	Yes
Pratzel et al. 1993 [16][b]	Yes	Yes	Yes	Yes	Yes
Pratzel et al. 1999 [11][c]	Yes	Yes	Yes	Yes	Yes
Franke et al. 2000 [20]	Yes	Yes	Yes	Yes	Yes
van Tubergen et al. 2001 [21]	Yes	Yes	Yes	Yes	Yes

[a]Method of randomization was not described in detail; blinding of patients not possible due to the method of treatment. No blinding of evaluator described. Dropouts and withdrawals (about 20%) during follow-up were not commented. Included for meta-analysis
[b]No dropouts or withdrawals reported. Included for meta-analysis
[c]No dropouts or withdrawals reported. Only data not reported in Pratzel 1993 were included for meta-analysis

One clinical trial [18] did not meet all the quality criteria. In it, Lind-Albrecht reported a prospective randomized controlled investigation of 100 patients with ankylosing spondylitis, comparing the effects of speleotherapeutic radon exposure or sauna treatment (randomized allocation) in addition to a standardized 3-week out-of-town rehabilitation program. Critical evaluation of the complete report in her thesis publication revealed that outcome measures in the follow-up period had been analyzed without providing adequate information on dropouts (about 20%). Although dropouts may have influenced results and statistical analysis, this clinical trial was included.

All 46 patients treated in Schlema and reported by Pratzel and coworkers in 1993 [16] were included. Their 1999 paper [11] again reported on these patients and on an additional 52 treated in a separate trial at Bad Steben. From the 1999 paper, we included only the 52 new patients.

Trials included for meta-analysis

Finally, five clinical trials with a total of 338 patients suffering from rheumatic diseases were accepted as meeting all inclusion criteria, i.e., they were prospective randomized controlled clinical trials comparing radon therapy with another intervention and reporting on pain intensity before and after treatment.

Descriptive summary of selected trials

Pratzel et al. 1993 [16]: a prospective randomized controlled double-blind trial (the scentless, inert radon gas qualifies best for double-blind studies) was conducted in 46 patients with painful noninflammatory disorders of the cervical spine during an out-of-town inpatient rehabilitation program. After nine immersions for 20 min each over 4 weeks in 36–37°C radon water with 3 kBq/L concentration or radon-free tap water (in addition to rehabilitation treatment), the analgesic effect was significant in both the radon and control groups (reduced pain on pressure, pressure threshold meter [19]), without a difference between groups, but 2 and 4 months after commencement of treatment, pain on pressure had significantly declined in the radon group as compared to the control group.

Pratzel et al. 1999 [11]: almost the same results were found after radon treatment had been administered to 52 patients with complaints due to degenerative spinal disorders or osteoarthritis of the large joints. Radon water at 0.8 kBq/L and 36–37°C was used for eight or nine immersions for 20 min each. The control group bathed in radon-free tap water at the same temperature. Pain on pressure was measured at 16 defined points on the patients' backs using the pressure threshold meter [19]. The mean of the 16 pain threshold measurements was used for statistical analysis. Four months after commencement of treatment, the radon group showed a significantly higher pain-on-pressure threshold than the control group.

Franke et al. 2000 [20]: this randomized controlled double-blind trial compared the effects on pain intensity (visual analogue scale) and functional restrictions (Keitel functional test and Arthritis Measurement Scales questionnaire) of 15 combined 35°C radon (1.3 kBq/L) and CO_2 (1.6 g/L) baths with CO_2 baths (1.6 g/L) at the same temperature in 60 patients with rheumatoid arthritis during and after a 4-week inpatient rehabilitation program. Both groups showed comparable baseline situations. After completion of treatment, clinical improvements were observed in both groups without notable group differences. The follow-ups revealed, however, sustained effects in the radon arms and a return to baseline levels in the sham arms. After 6 months, significant differences between the groups were found for both endpoints, pain and function, in favor of the radon group.

Van Tubergen et al. 2001 [21]: this randomized controlled trial evaluated three groups of 40 patients each. All patients suffered from ankylosing spondylitis. Three consecutive weeks of spa exercise therapy, including either ten radon-thermal treatments in the galleries of the Gasteiner Heilstollen in Austria (group 1) or ten sauna treatments (group 2), followed by 37 weeks of weekly group physical therapy were compared to weekly group physical therapy alone (group 3). Outcome variables were functional ability, patient overall well-being, pain, and duration of morning stiffness; a pooled index of change was used for statistical analysis. Compared to the control group at 28- and 40-week follow-ups, the improvement from baseline values was significantly better in the radon group but not in the treatment group without radon exposure. For the present meta-analysis, only data of both spa exercise groups (with radon or sauna treatment) were included (disregarding data of group 3).

Lind-Albrecht 1994 [*18*]: a prospective randomized controlled trial with 100 patients suffering from ankylosing spondylitis compared the effects of speleotherapeutic radon exposure in the Bad Kreuznach cave (Germany) with those of sauna treatment in addition to a standardized 3-week out-of-town rehabilitation program. Immediately after treatment, most (primary and secondary) outcome parameters such as pain, mobility, posture, lung function, and general health status were found improved in both treatment groups, but no statistically significant difference was observed between the radon and sauna groups. At the first follow-up 3 months after completion of therapy, however, a significant difference in pain reduction was found in favor of the radon group.

Meta-analysis

The analysis of pooled data on pain reduction obtained from 338 patients showed no significant difference between radon and control therapy immediately after treatment (*P*=0.13) (Fig. 1). In follow-ups, the overall effect on pain reduction was significantly better in the radon group 3 months (*P*=0.02) (Fig. 2) and 6 months (*P*=0.002) (Fig. 3) after treatment.

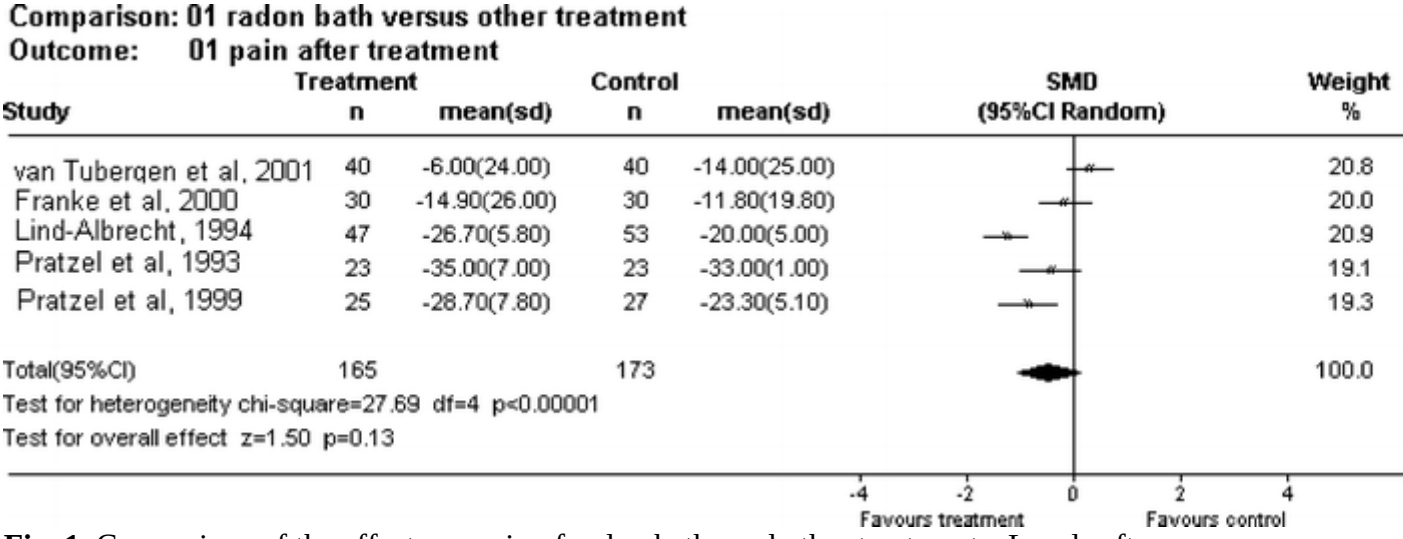

Fig. 1 Comparison of the effects on pain of radon baths and other treatments. Levels after treatment. *SMD* standard mean difference

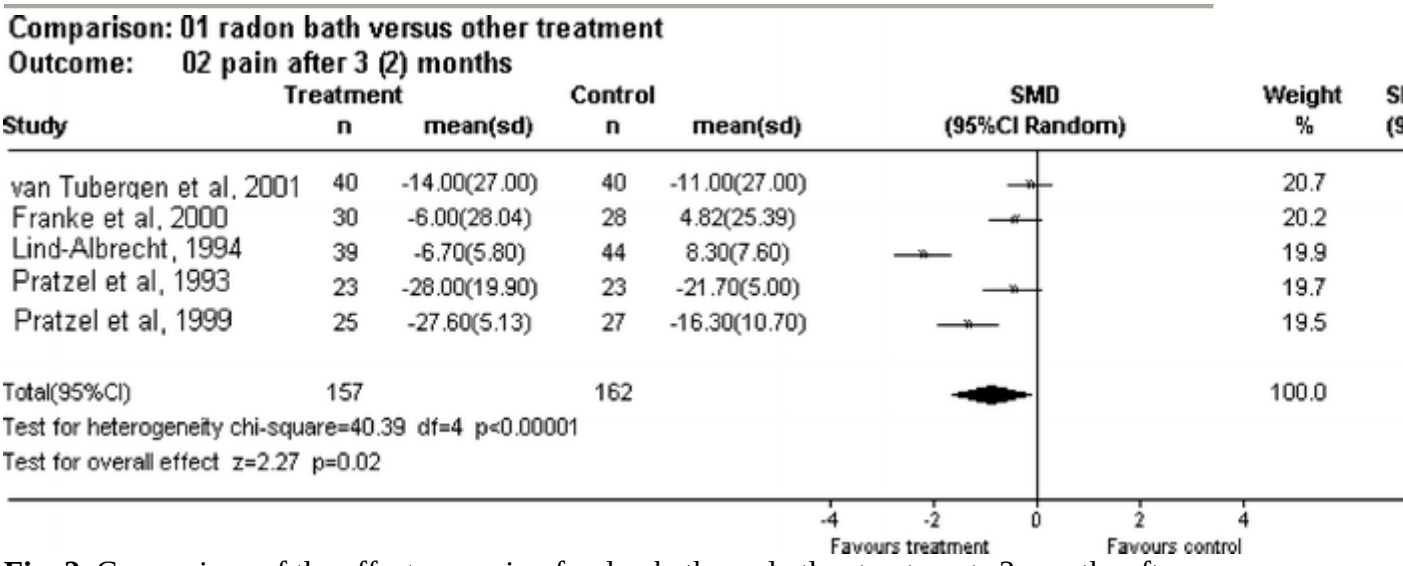

Fig. 2 Comparison of the effects on pain of radon baths and other treatments 3 months after treatment. *SMD* standard mean difference

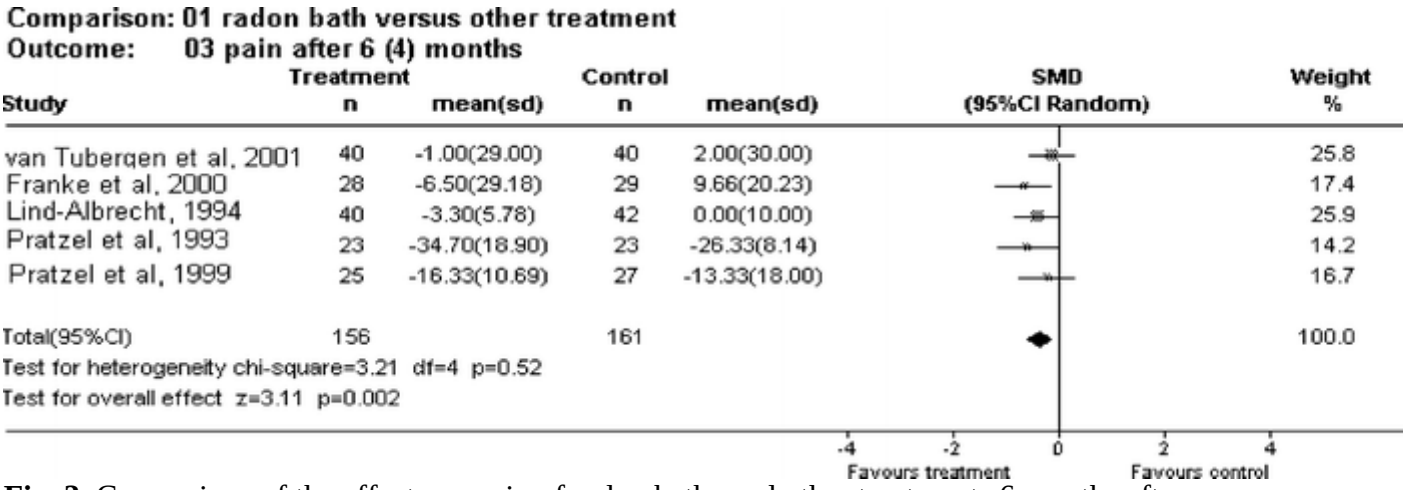

Fig. 3 Comparison of the effects on pain of radon baths and other treatments 6 months after treatment. *SMD* standard mean difference

Discussion

Controlled clinical trials on the effects of radon therapy for the treatment of rheumatic diseases are rare. The five trials meeting the inclusion criteria, three of them with a double-blind study design, showed beneficial effects of radon therapy as compared to interventions without radon exposure. Differences between radon therapy and control interventions were not significant at the end of treatment phases. In the following months, however, the interventions including radon showed significantly better pain reduction than did those without radon.

The radon concentrations in radon baths were 0.8 kBq/L [11], 1.3 kBq/L [20], or 3 kBq/L [16]. The radon concentration in air was up to 160 kBq/m^3 in the galleries of the Gasteiner Heilstollen [21] and 37–130 kBq/m^3 in Bad Kreuznach [18]. From these few trials, no conclusion can be drawn with regard to the optimum radon concentration.

One limitation of this systematic review may arise from the fact that pain caused by various rheumatic diseases was pooled for meta-analysis. However, pain is a highly subjective experience that shows common features despite different eliciting causes. We followed existing proposals for selecting and appraising studies for a systematic review [44, 45] and accepted only studies that compared radon exposure with other treatment modalities.

The existing randomized controlled trials suggest a positive effect of radon therapy on pain in rheumatic diseases. With respect to the potential clinical effect and given the increasing public interest in radon therapy for the treatment of rheumatic diseases, there is an urgent need for further controlled clinical investigations.

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