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ORIGINAL ARTICLE

Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre IMuRa trial

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Abstract In chronic rheumatic diseases, recent treatment regimens comprise multimodal concepts including pharmacologic, physical/exercise, occupational and psychological therapies. Rehabilitation programmes are used for long-term management of disease. Spa therapy is often integrated in various middle and south European and Asian countries. Here, we investigated radon spa therapy as applied in health resorts compared to a control intervention in rheumatic out-patients. Randomised, blinded trial enroling 681 patients [mean age 58.3 (standard deviation 11.1); female 59.7 %] in 7 health resorts in Germany and Austria with chronic back pain ($n_1 = 437$), osteoarthritis (OA) ($n_2 = 230$), rheumatoid arthritis ($n_3 = 98$), and/or ankylosing spondylitis ($n_4 = 39$); multiple nominations in 146 cases). Outcomes were pain (primary), quality of life, functional capacity, and medication measured before start, after end of treatment, and 3 times thereafter in 3 monthly intervals. Adverse events were documented. To analyse between-group differences, repeated-measures analysis of covariance was performed in metric endpoints and Fisher's exact test in rates. Two-sided significance level of 5 % was chosen. Until end of follow-up, superiority of radon therapy was found regarding pain relief ($p = 0.032$) and analgesic drug consumption ($p = 0.007$), but not regarding quality of life. Functional capacity was assessed specific to the underlying indication. Significant benefits were found in radon-treated OA patients until 6-month follow-up ($p = 0.05$), but not until end of study ($p = 0.096$). Neither the back pain sub-population nor the two smaller patient populations with inflammatory indications benefited significantly in functional capacity. Results suggest beneficial analgesic effects of radon spa therapy in rheumatic diseases until 9 months post-intervention.

Keywords Randomised controlled trial · Radon spa therapy · Chronic rheumatic diseases · Long-term benefits · Pain relief · Reduced analgesic drug consumption

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Introduction

In chronic rheumatic diseases, recent treatment regimens comprise multimodal concepts including pharmacologic, physical/exercise, occupational and psychological therapies to support the long-term management of disease. Spa therapy is often integrated in middle and south European and Asian countries although little used in Anglo-saxon and Scandinavian ones.

Since the beginning of the twentieth century, the chemically inert naturally radioactive gas radon has been applied therapeutically in rheumatology [1]. Many patients are treated every year in countries with a tradition of radon spa therapy, i.e. Austria, Germany, Poland, the Czech Republic, Italy, Russia, or Japan. While in Russia and Asia various diseases besides rheumatic ones (e.g. pulmonary, cardiovascular or diabetes) were treated, the main indication in Europe is rheumatic conditions. Here, nearly all research activities concentrated on and all publications cited referred to musculoskeletal disorders. Most recent evidence on the effectiveness of spa therapy in rheumatic disorders was

summarised by systematic reviews [2–6] published between 1997 and 2007. They were based on several randomised controlled trials (RCT) [7–14] mainly performed between 1993 and 2004. Since about 2000, nearly no institutional research infrastructure on spa therapy exists anymore in Germany and only very few worldwide (Austria, France, Hungary, Turkey, Russia, Japan for example). So, most of the few RCT performed (other than [11, 14]) were medical dissertations and not published properly to grant easy access for the public. Even older observational studies were mainly published in conference proceedings, special series, see [15], or books from non-commercial publishers, e.g. [16]. In 1997 (see [16]) for instance, articles on pain relief, anti-inflammatory [17], immune modulating [18, 19], and anti-proliferative effects [20, 21] of radon were reported. Most journal essays, e.g. on associations with stimulated production of cortisol [22], enhanced levels of endorphins, noradrenalin, serotonin and TGF-β [23, 24], reduced release of oxygen radicals [25], and influence of immune-competent cells of the skin [26, 27] were published before 2000.

Although empirical experience has referred to sustained analgesic effects for decades now, clinical evidence according to modern standards is no easily available.

To date, the German health care system supports radon therapy within rehabilitative treatment—settings of most of the RCTs cited. However, in out-patient settings, radon treatment is not re-financed by statutory health insurances, since it is not yet acknowledged as a stand-alone treatment option in the German "Heilmittelrichtlinie" (guideline of sufficient, useful, and economic care) established by statutory health insurances and the federal physicians' association (see social legislation §92 SGB V).

Therefore, we designed a pragmatic, randomised, blinded trial aimed at comparing radon spa therapy (Rn) versus a comparable radon-free (control) treatment in an outpatient setting for usual care purposes and without synchronous treatment options other than continuation of long-term and stable therapies before trial's start. Four major indications in rheumatology were addressed: chronic back pain (BP), degenerative osteoarthritis (OA), rheumatoid arthritis (RA), and/or ankylosing spondylitis/other spondylarthropathies (AS). We expected superiority of radon spa therapy in relieving rheumatic pain over several months. Additional treatment effects might be reached in reduced medications, quality of life, and/or function.

Methods

Study design

The trial with 2 parallel groups (randomised 1:1) was performed in 7 certified health resorts in Germany and Austria which are known for natural springs containing radon in therapeutically relevant concentrations and/or providing radon speleotherapy. For the externally performed randomisation, a computer-generated random allocation sequence was provided. Randomisation was stratified by centre, rheumatic indication, and initial pain level. Investigator, therapists, and patients were blinded to treatment, except for those who received speleotherapy or the respective control.

Administrational/technical staff without patient contacts ensured the correct allocation of baths according to individual time tables of patients. Unblinding was not performed before the last follow-up. Although an emergency procedure existed for premature unblinding on investigator's decision, there was no need to use it.

The leading ethics committee (of the Saxonian Medical Association, Dresden, Germany) as well as the respective regional ethics committees of participating investigators approved the protocol. Written informed consent was obtained from all patients.

Patients

Patients with at least one of the following conditions were included: BP of degenerative pathology or osteoporosis, OA of hip and/or knee joint(s), RA and/or ankylosing spondylitis/other spondylarthropathies (AS). No detailed confirmation procedure regarding their diagnosis was performed because recruitment was done by family doctors who knew patient's history of disease quite long before the start of trial and due to budget limitations. All participants lived in/near to the respective health resort to ensure the follow-up visits as planned. Furthermore, chronic or recurrent pain lasting longer than 6 months and mean pain levels ≥ 3 on initially assessed numeric rating scales (NRS) were requested. Patients were excluded if they had received any radon therapy during the preceding 9 months. Age >18 years and sufficient knowledge of German language were required. Exclusion criteria were advanced cardiac insufficiency (above NYHA II), hypertension grad 3, severe ventricular arrhythmia, myocardial infarction or stroke, known thermal urticaria, any contraindication against whole-body thermo-neutral water immersion, current exacerbations of the inflammation in inflammatory rheumatism, malignant tumours under current oncologic treatment, pregnancy, acute infections, or other generally accepted contraindications against spa therapy. Ads in local newspapers, on websites or via family doctors were used to find patients. If allocated to the control arm, patients were offered later radon applications to enhance willingness to participate and ensure compliance until the end of trial.

Interventions

Study treatment consisted of 12 regional-specific radon baths applied within 3–4 weeks (every 2–3 days) of 36–38 °C and 20 min duration, with equally long rest thereafter), or tap water baths under the same conditions. In Bad Brambach, the spring water contains radon and carbon dioxide, and therefore, the control group received tap water baths charged with artificial CO_2, see [10, 14]. In Bad Steben, extract of spruce needles was added to blind patients against the specific colour and odour of the natural spring water [9]. In Bad Gastein, 10× radon speleotherapy (within 3 weeks) were given and compared to a series of so-called "soft vapour-baths" (producer: Co. Silgmann) allowing 37–41.5 °C and 70–99 % humidity to provide comparable conditions like in gallery visits.

Slight adaptations of dose and frequency, e.g. due to short-term intercurrent diseases, were allowed. In case of hypersensitive reactions or other adverse events (AEs) adequate medical care and short-term interruption of study intervention (if necessary) were allowed. Interruptions of >4 weeks would have led to premature termination of treatment (not of observation) but did not occur within the trial.

If stable medications and/or physical therapies were regularly used since ≥3 months before randomisation these were allowed to be continued during treatment. Because of the sufficiently large samples, randomised group allocation and the delayed effect of radon, we expected no bias between groups. All additional short-term interventions were to be avoided or at least discussed with the principle investigator.

Outcomes

Main outcome measures were self-assessed pain levels for current, average, and maximum pain (3 NRS with codes from 0 to 10) within the last 7 days. Numeric rating scales were used as advocated by "Deutscher Schmerzfragebogen" of the German Pain Society [28]. Patients had to complete separate sheets for every assessment to ensure unawareness of their exact former assessment. Means of all 3 scales for every time point were calculated. The change in scores with respect to baseline level was used in confirmatory analysis. Secondary endpoints were physical and mental health composite scores (PCS/MCS) of the SF-12 questionnaire [29] where scores of 40–60 limit the normal range of health-related quality of life (QoL) within the general German population and 100 indicates the optimum. Indication-specific questionnaires on functional capacity were applied—(1) Hannover Functional Capacity Questionnaire (FFbH-R; [30]) in BP, (2) Western Ontario and McMaster Universities Questionnaire (WOMAC; [31]) in OA, (3) Health Assessment Questionnaire (HAQ; [32]) in RA, and (4) Bath Ankylosing Spondylitis Functional Index (BASFI; [33]) in AS. All questionnaires represent valid and reliable standard assessments within the indications used and were scored according to authors' guidelines. Furthermore, patients were requested to report all intercurrent events (e.g. hospitalisations or short-term treatments), AEs, and all drug consumption/concomitant therapies independent of any relation to rheumatic indication with names, concentrations, and tablet counts (at best). This was done since no supervision by physicians could be organised during the trial due to limited resources. The aim was to avoid underestimation of consumption. A post hoc review of medication data was performed by an experienced physician who categorised the drugs as belonging to (1) non-steroidal antirheumatic drugs (NSAID) incl. coxibe, analgesics, or corticosteroids, (2) acetylic salicylic acid (ASA) and other platelet aggregation inhibitors, (3) disease-modifying antirheumatic drugs (DMARD), (4) biologics, and others (used for concomitant diseases). A semi-quantitative concept for analysis was applied to describe changes in drug consumption. For NSAID/analgesics we hypothesised a mid-term reduction after radon treatment. DMARD/biologics were assessed for description of trial population only.

Semi-quantitative concept of analysis:

- Per patient, time point and named drug, the daily dose was calculated from tablet count and concentration with missing value imputation based on (1) mean individual values from other time points or (2) mean of all nominations of the specific drug. When no details were given for a patient but noted "on request" half of the tablet count was used.
- Individual differences between baseline and all post-intervention doses averaged were categorised to reduced (i.e. −1), unchanged (0) or increased daily consumption (+1). If more than one medication of a class of drugs was consumed the classified changes were summed up to compensate a possible increase of one and reduction of another drug.
- Binary outcome regarding reduced post-treatment doses was analysed.

Outcomes were measured before start (T0), after end of treatment (T1), and every 3 months for the next 9 months (T2–T4).

Sample size estimations

We assumed modest between-group differences based on former radon trials using standard deviations of 14–18 mm VAS and effect sizes of 3–6 mm in various scenarios due the unknown ratio of participants' indications, and further sources of heterogeneity. Given a two-sided significance

level of 5 % and a power of at least 80 %, about 250 patients per treatment arm were required. Taking a 20 % drop-out rate into account, about 600 patients were planned for inclusion.

Statistical methods

Primary analysis was performed on an intention-to-treat basis. All randomised patients with at least one study intervention were included (full-analysis set according to ICH E9 guideline [34]). In case of missing pain assessment, a substitution was performed independently from treatment arm and according to a pre-defined conservative strategy:

> For missing values at the start of intervention the post-treatment value were used as baseline in sense of a "last observation carried forward" method. Similarly, missing post-treatment values were replaced by pre-treatment ones. If follow-up values were missing group-related mean changes were added to individual post-treatment values or linear interpolation was performed if suitable.

Repeated-measures analyses of covariance (RM-ANCOVA) were performed with changes in pain and pain baseline scores as covariate. Differences between treatment groups and classes of indications were analysed. Different courses of pain development within both treatment arms were considered, too, by the treatment-course interaction, according to study protocol. Four classes of indications were used: (1) BP only, (2) OA only—both presented frequently enough to ensure sufficient power for detailed sub-analyses, (3) RA or AS (combined: inflammatory rheumatism), (4) multiple inclusion diagnoses. Pre-conditions of the statistical method were approved and deviations adequately handled (by Huynh–Feldt epsilon correction of degrees of freedom [35]).

A hierarchical analysis strategy with multiple tests was followed to identify the time period of potential treatment differences and examine long-term effects [36] without α-adjustment. Based on previous evidence that treatment effects occur some weeks after the end of intervention, data up to 3 months was analysed first. Only in case of significant treatment differences or significantly different pain courses under both treatments (interaction) the data of the next follow-up was added in following analyses. Interim analysis was neither planned nor done.

QoL and functional endpoints were analysed similarly. Rates of reduced medications were compared by Fisher's exact test, presented with 95 % confidence intervals (CI), and—if significant—with numbers needed to treat. Safety outcomes were analysed descriptively. Statistical analyses were done with SPSS.

Results

Patient flow

The trial started in April 2009 and ended in June 2011 (last patient's last visit). Of 681 patients screened 652 comprised the full-analysis population (Fig. 1). Screening failures were: concomitant diseases (6×), job-related (3×), private incl. too time-consuming/too expensive (5×), refusal of control arm (3×; in Badgastein), not given (12×).

The numbers of patients included per centre were (control/radon):

- Bad Brambach (D): 50/52.
- Bad Hofgastein (A): 34/33.
- Bad Schlema (D): 58/60.
- Bad Steben (D): 53/54.
- Bad Zell (A): 26/25.
- Badgastein radon gallery (A): 72/75.
- Menzenschwand (D): 27/33.

In Badgastein, more withdrawals during the course of trial occurred, too (see Fig. 1).

Baseline characteristics

Table 1 summarises characteristics of the groups and shows only minor discrepancies. About 60 % of participants were women; mean age was 58.3 (standard deviation: SD 11.1) years. The number of patients with BP was $n_1 = 437$ (67 %), with OA $n_2 = 230$ (35 %), with RA $n_3 = 98$ (15 %), and with AS $n_4 = 39$ (6 %) (including multiple nominations). 146 cases reported multiple inclusion diagnoses, 89 suffered from inflammatory rheumatism while 307 resp. 110 participants presented with BP and OA alone. 461 of 652 patients documented medications (see Table 1).

Protocol compliance

All patients fulfilled the in-/exclusion criteria and were treated within the randomised arm without premature unblinding. For the pain assessments, 3 baseline scores and few sequels (max 7.7 %) were missed and imputed for confirmatory analysis. In the SF-12, single items were missed quite frequently resulting in the smaller samples (see Table 2). Functional assessment of BP patients was not available in 2.0–9.8 % at different follow-ups. In OA this was true for ≤17.5 %, in RA for ≤13.3 % and in AS for ≤10.2 % (without remarkable group differences).

Median (25; 75 %) duration of treatment was 27 [22; 34] days in the radon and 26 [21; 30] days in the control group. Mean numbers of tube baths (and SD) were 11.8

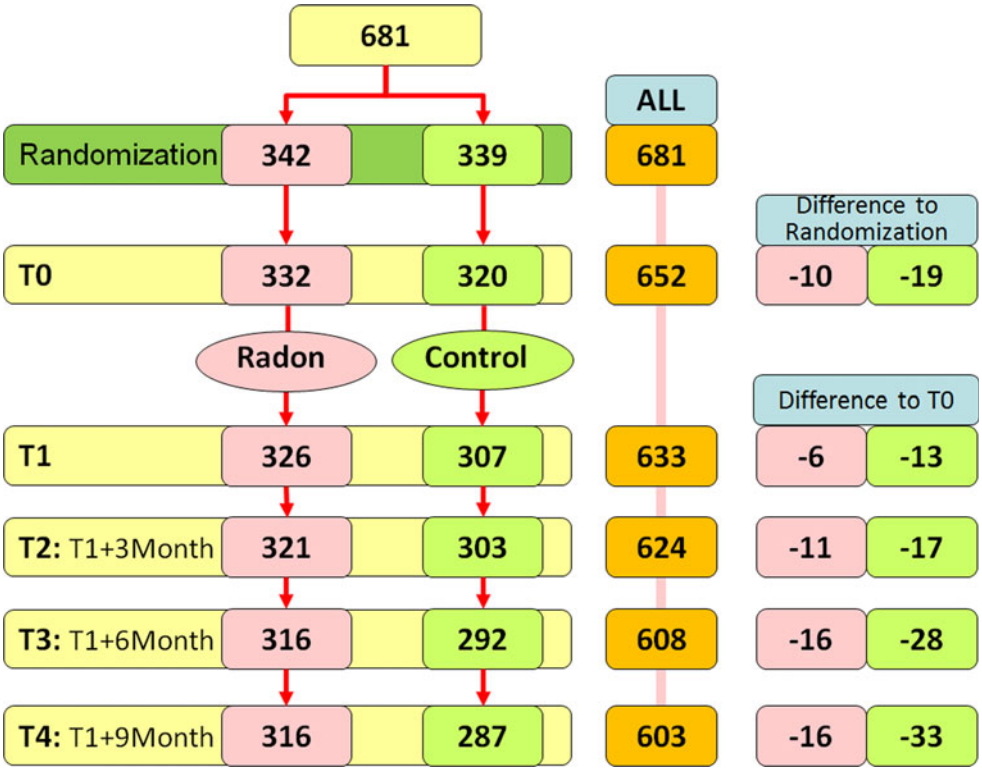

Fig. 1 Patients' flow in the IMuRa trial (with sample sizes per group and time point; *T0* before start of treatment; *T1* after end of treatment)

(0.8) resp. 11.8 (1.0). Fewer baths than planned were applied in 15 radon patients (i.e. 5–11) and in 9 control patients (1–10). In Badgastein, 10 (0.2) gallery visits were applied versus 9.7 (1.5) vapour-baths with 5 patients receiving erroneously 1–12 baths. No group discrepancies of treatment intensity were found.

After end of treatment patients were asked which treatment they supposed they had received. A total of 431/505 patients (without Badgastein) answered the question. Only 239 (55 %) correctly identified their treatment (95/144 for the radon/control arm).

Endpoints

The endpoints including the results of statistical tests are shown in Table 2.

Confirmatory analysis of pain assessments

A significant superiority regarding pain relief was seen after radon spa therapy during the total course of observation. Despite a slight decline between 3 and 9 months into follow-up, the radon group showed a more pronounced pain relief as compared to control, although even the control group showed benefits compared to baseline level (Fig. 2). Figure 3 presents the pain situation within the different indications and reveals that patients with multiple rheumatic indications and inflammatory rheumatism suffered from more pain than the other groups and nearly returned to baseline levels after 9 months of follow-up. Nearly no effect of the control treatment series could be observed in inflammatory rheumatism.

Secondary analyses of quality of life, functional capacity, and drug intake

No significant group differences regarding the physical and mental component of QoL were found. Regarding the latter, the study samples were within the populations' normal range from start to end of the observations.

Significant functional benefits were found in OA patients after radon therapy until 6 months into follow-up ($p = 0.05$) but not until the end of the study ($p = 0.096$). Neither the back pain sub-population nor the two smaller patients' populations with inflammatory indications benefited significantly in functional capacity.

Rates of patients with significantly reduced post-treatment intake of NSAID/analgesic medication were 47 [95 % CI 40; 54] % after radon compared to 34 [95 % CI 28; 40] % ($p = 0.007$) after control treatment (Fig. 4). This group difference resulted in a number needed to treat to gain one more patient with reduced intake of 7.6 [95 % CI 4.5; 25.7] %—a relevant effect in favour of radon. ASA dose reduction was observed in 38 [95 % CI 27; 50] % of radon patients and 24 [95 % CI 13; 37] % of control patients resulting in a non-significant p value of 0.145.

Table 1 Patient characteristics of the study population

Characteristics	Control group ($n = 320$)[a]	Radon group ($n = 332$)[a]	Total ($n = 652$)[a]
Indications (multiple nominations possible)			
Back pain (BP)	214	223	437
Osteoarthritis (OA)	119	111	230
Rheumatoid arthritis (RA)	50	48	98
Ankylosing spondylitis (AS)	19	20	39
Multiple indications	78	68	146
Female, no (%)	194 (60.6)	195 (58.7)	389 (59.7)
Within BP sub-population	90	104	
Within OA sub-population	32	32	
Within RA sub-population	21	21	
Within AS sub-population	3	4	
Within Multiple indications sub-population	48	34	
Age, mean (SD)[a], years	58.1 (10.7)	58.5 (11.5)	58.3 (11.1)
Within BP sub-population	62.2 (11.9)	57.1 (11.1)	
Within OA sub-population	59.4 (9.2)	58.6 (11.9)	
Within RA sub-population	56.4 (11.4)	54.9 (11.3)	
Within AS sub-population	59.6 (12.9)	60.5 (17.1)	
Within Multiple indications sub-population	61.6 (10.4)	63.5 (9.7)	
Body mass index, mean (SD)[a], kg/m^2	27.8 (4.6)	27.2 (5.0)	27.5 (4.8)
Live in family context, no (%)	225 (70.3)	233 (70.2)	458 (70.2)
Employment status, no (%)[b]			
Employed (full or part-time)	144 (45.0)	152 (45.8)	296 (45.4)
Retired	16 (5.0)	14 (4.2)	30 (4.6)
Unemployed	87 (27.2)	97 (29.2)	184 (28.2)
Application for pension, no (%)[a]	14 (4.4)	16 (4.8)	30 (4.6)
Risk factors, no (%)[a]			
Smoking	41 (12.9)	45 (13.6)	86 (13.2)
Overweight	155 (48.6)	137 (41.3)	292 (44.9)
Poverty of motion	79 (24.8)	61 (18.4)	140 (21.5)
Stress/hectic pace	99 (31.0)	105 (31.6)	204 (31.3)
Hypertension	96 (30.1)	90 (27.1)	186 (28.6)
High cholesterol level	78 (24.5)	72 (21.7)	150 (23.0)
High alcohol consumption	11 (3.4)	9 (2.7)	20 (3.1)
High drug consumption	20 (6.3)	25 (7.5)	45 (6.9)
Diabetes	20 (6.3)	28 (8.4)	48 (7.4)
Study-relevant medications, no (%)	221 (69.1)	240 (72.3)	461 (70.7)
Thereof: with NSAID/analgesics	207 (64.7)	215 (64.8)	422 (64.7)
Thereof: with DMARD	19 (5.9)	30 (9.0)	49 (7.5)
Thereof: with ASA	42 (13.1)	66 (19.9)	108 (16.6)
Thereof: with biologics	9 (2.8)	8 (2.4)	17 (2.6)
Primary endpoint	$n = 317$	$n = 332$	$n = 649$
Pain assessment, NRS, at baseline, mean (SD)	5.45 (1.71)	5.63 (1.55)	5.54 (1.63)
Within BP sub-population	5.44 (1.74)	5.64 (1.52)	
Within OA sub-population	5.20 (1.66)	5.61 (1.47)	
Within RA sub-population	5.16 (1.70)	5.75 (1.61)	
Within AS sub-population	5.50 (2.18)	5.35 (1.66)	
Within Multiple indications sub-population	5.78 (1.60)	5.60 (1.67)	

Table 1 continued

Characteristics	Control group ($n = 320$)[a]	Radon group ($n = 332$)[a]	Total ($n = 652$)[a]
Quality of life: SF-12 at baseline, mean (SD),	$n = 239$	$n = 228$	$n = 467$
Physical health composite Score: PCS	36.3 (9.4)	37.6 (8.6)	36.9 (9.0)
Mental health composite Score: MCS	49.8 (10.4)	49.9 (10.3)	49.8 (10.3)
Functional capacity/limitations at baseline, mean (SD),			
BP: FFbH-R [max. 100 → best]; $n = 213 + 215$	64.9 (21.6)	68.0 (21.1)	66.5 (21.3)
OA: WOMAC [max. 10 → worst]; $n = 105 + 101$	3.9 (1.9)	3.9 (1.9)	3.9 (1.9)
RA: HAQ [max. 3 → worst]; $n = 48 + 45$	0.95 (0.62)	0.93 (0.52)	0.94 (0.57)
AS: BASFI [max. 10 → worst]; $n = 19 + 19$	3.9 (2.3)	3.6 (2.0)	3.8 (2.1)

No: number of patients; SD: standard deviation; NSAID: non-steroidal antirheumatic drugs including coxibe, analgesics, and/or corticosteroids; DMARD: disease-modifying antirheumatic drugs; ASA: acetylic salicylic acid or other platelets' aggregation inhibitors; NRS: mean of 3 NRS/primary endpoint; SF-12: Medical outcome study 12-item short-form health status survey to measure health-related quality of life

[a] Due to missing data, actual sample sizes may be somewhat smaller (range 1–11 %)

[b] Not all categories given

Safety analysis

During the period of study intervention 32 patients reported an AE but 6 of them did not refer to AEs in a narrower sense, e.g. disease/surgery of the husband, leaving of the treating physician, too time-consuming study procedures or no clinical improvement. In only 7 events was the timing clearly attributed to the treatment phase. In unclear time-event relationship we regarded the reported events conservatively as AE.

Of 26 clinical AEs in 19 events causality to intervention was regarded at least possible, 13 within the radon group and 6 within the control group. Possible adverse reactions named more than once referred to (radon/control) were

- Aggravation of pain: 7/1,
- Hypertension: 2/1,
- Fatigue: 2/1, and
- Coloured skin/nails: 2/0.

All AEs were of mild or moderate severity and resolved within few hours/days.

Hospitalisations occurred in 3 patients but in only one case could the admission be verified as during the treatment series. None of these admissions was causally related to study treatment and no other serious adverse reactions occurred.

Discussion

Our study is the largest and most comprehensive radon RCT comparing radon spa therapy to radon-free treatment in rheumatic disorders. It demonstrated that radon spa therapy is superior to radon-free control treatment regarding pain relief in an outpatient setting. Although the averaged absolute change is below 1 point on the pain scale and the between-group difference is even smaller, a significantly reduced intake of NSAID/analgesic drugs was observed during a post-intervention period of 9 months. Regarding the long history of disease in most rheumatic patients, a more pronounced improvement is not to be expected from 12 baths or 10 gallery visits. Our results on pain relief are in general accordance with those of systematic reviews on radon spa therapy [3–6] based on former RCTs in rheumatic disorders, although primarily trials in inflammatory rheumatism ([10, 14] in RA; [8, 11] in AS) contributed to benefits of radon therapy presented there. Various trials in rheumatic pain from degenerative causes might have included too few patients to reach significance [9, 37] or have been tainted by methodological flaws, e.g. chosen a question of equivalence while using statistical methods to test superiority [12, 13] to provide additional evidence in systematic reviews. With sufficiently large sample sizes, it might be possible to show superiority of radon treatment in degenerative indications like BP and OA, too, since most of our patients suffered from those disorders. Similarly, reduced analgesic consumption was formerly reported by Lind-Albrecht [38] in AS and by Franke et al. [14] in RA which might correspond with lower risk of known side effects.

A further interesting finding of the trial is that the maximum pain relief was observed at 3 months into follow-up in *both* arms although—in contrast to most radon trials—this one was performed in an outpatient setting without systematic concomitant intervention. A delayed maximum pain relief after radon intervention was expected based on existing evidence. But, here, we found a similar course in the control group which is not easily explained without speculation. Nevertheless, two further trials which investigated pain in degenerative rheumatic disorders and compared

Table 2 Outcomes with baseline and change scores and ANCOVA results

Outcome	Control group	Radon group	RM-ANCOVA *p* value of treatment difference (TME)	RM-ANCOVA *p* value of differences between indications (IME)	RM-ANCOVA *p* value of different courses under both treatments (TxC)
Confirmatory analysis (FAS)					
Pain assessment, mean (SD)	320 pts.	332 pts.			
Baseline score	5.44 (1.71)	5.63 (1.55)	(model until…)	(model until…)	(model until…)
CS, End of treatment	0.23 (1.60)	0.56 (1.67)			
CS, 3 months' FU	0.52 (1.86)	0.91 (1.90)	**0.012**$^{\$}$	**0.008**	0.636
CS, 6 months' FU	0.49 (1.82)	0.84 (1.97)	**0.011**$^{\$}$	**0.015**	0.883
CS, 9 months' FU	0.48 (1.94)	0.76 (1.95)	**0.032**$^{\$}$	**0.005**	0.413
Secondary analyses^{+}					
Health-related quality of life					
PCS of SF-12, mean (SD)	239…173^{++} pts.	228…168^{++} pts.		297/247/207 pts.	
Baseline score	36.28 (9.41)	37.60 (8.55)	(model until…)	(model until…)	(model until…)
CS, end of treatment	−1.22 (5.82)	−1.52 (7.72)			
CS, 3 months' FU	−2.32 (7.44)	−2.88 (8.49)	0.154	**0.045**	0.395
CS, 6 months' FU	−1.67 (8.52)	−2.70 (8.81)	0.142	0.139	0.422
CS, 9 months' FU	−2.41 (7.90)	−2.28 (8.45)	0.181	0.204	0.761
MCS of SF-12, mean (SD)	239…173^{++} pts.	228…168^{++} pts.		297/247/207 pts.	
Baseline score	49.76 (10.38)	49.92 (10.27)	(model until…)	(model until…)	(model until…)
CS, end of treatment	−1.04 (9.44)	−1.09 (9.21)			
CS, 3 months' FU	−0.99 (9.78)	−1.41 (9.52)	*0.058*	0.396	0.562
CS, 6 months' FU	−0.74 (10.20)	−0.57 (9.80)	0.284	0.731	0.954
CS, 9 months' FU	0.74 (8.54)	−0.15 (9.38)	*0.097*	0.907	0.904
Functional capacity/limitations					
In BP: FFbH-R, mean (SD)	213…189^{++} pts.	215…205^{++} pts.		in BP 406/393/382 pts.	
Baseline score	64.86 (21.56)	68.02 (21.05)	(model until…)		(model until…)
CS, end of treatment	−0.07 (10.75)	−1.47 (13.22)			
CS, 3 months' FU	−0.75 (13.79)	−1.90 (13.50)	*0.076*		0.847
CS, 6 months' FU	0.76 (14.40)	0.52 (14.96)	0.226		0.517
CS, 9 months' FU	0.86 (14.14)	−0.09 (14,04)	0.213		0.512
In OA: WOMAC, mean (SD)	105…91^{++} pts.	101…93^{++} pts.		in OA 198/182/172 pts.	
Baseline score	3.9 (1.9)	3.9 (1.9)	(model until…)		(model until…)
CS, end of treatment	0.10 (1.49)	0.46 (1.48)			
CS, 3 months' FU	0.33 (1.73)	0.56 (1.64)	*0.096*		0.680
CS, 6 months' FU	0.31 (1.79)	0.50 (1.68)	**0.050**		0.743
CS, 9 months' FU	0.45 (1.55)	0.32 (1.90)	*0.092*		0.308
In RA: HAQ, mean (SD)	48…41^{++} pts.	45…42^{++} pts.		in RA 81/79/76 pts.	
Baseline score	0.95 (0.62)	0.93 (0.52)	(model until…)		(model until…)
CS, end of treatment	0.10 (0.29)	0.08 (0.39)			

Table 2 continued

Outcome	Control group	Radon group	RM-ANCOVA *p* value of treatment difference (TME)	RM-ANCOVA *p* value of differences between indications (IME)	RM-ANCOVA *p* value of different courses under both treatments (TxC)
CS, 3 months' FU	0.08 (0.31)	0.10 (0.42)	0.731		0.558
CS, 6 months' FU	0.07 (0.43)	0.17 (0.37)	0.461		0.312
CS, 9 months' FU	0.07 (0.34)	0.09 (0.45)	0.453		0.418
In AS: BASFI, mean (SD)	19 pts.	19…16^{++} pts.		in AS 37/35/35 pts.	
Baseline score	3.9 (2.3)	3.6 (2.0)	(model until…)		(model until…)
CS, end of treatment	−0.11 (0.86)	−0.24 (1.49)			
CS, 3 months' FU	−0.08 (0.79)	−0.10 (1.59)	0.805		0.654
CS, 6 months' FU	−0.22 (1.01)	−0.52 (1.63)	0.871		0.340
CS, 9 months' FU	0.22 (0.92)	−0.26 (1.24)	0.639		0.252

TME: treatment main effect in analyses of covariance; IME: indication main effect in analyses of covariance; TxC: treatment-course interaction in analyses of covariance; FAS: Full-analysis set of all randomised patients with at least 1 study treatment following the intention-to-treat principle; CS: Change score = difference of baseline minus course score; bold: *p* values <0.05, significances; italics: *p* values <0.10, borderline significances; FU: follow-up; PCS: physical health composite score; MCS: mental health composite score; BP: chronic back pain; OA: osteoarthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis

$ According to hierarchically ordered hypotheses, significant main effects or interactions are necessary to add the next point in time to the model

+ Significance levels should be interpreted "descriptively"; …*n* pts.: sample size per FU which differs due to missing items/questionnaires between the *n*'s given

++ No replacement strategy for missing values

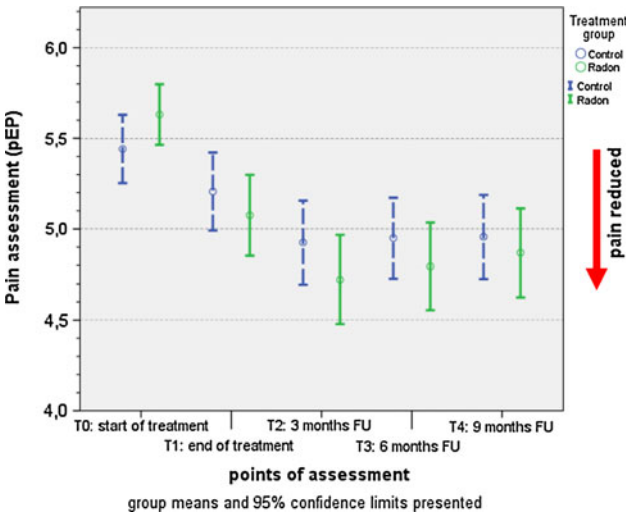

Fig. 2 Self-assessed pain (mean and 95 % confidence interval) for the treatment groups (*pEP* primary endpoint, *FU* follow-up)

radon versus placebo baths in a blinded way ([7; 9]) showed an analogous phenomenon in both arms with most pronounced effects 2 months after end of treatment. Further research is needed to clarify this finding.

The secondary endpoints—quality of life and functional capacity—did not result in benefits regarding radon spa therapy on the whole. A gain of functional capacity was observed only in OA patients up to 6 months post-treatment, but not at the end of the study.

Protocol adherence was satisfying regarding (1) willingness of patients to dedicate costs/efforts of their own (e.g. travel and time; without reimbursements) against their risk of receiving sham treatment, (2) empathy of participating centres to provide all therapies and logistics, and (3) engagement of study nurses to realise study logistics and documentation issues beside their regular duties. Weaknesses of the trial to be named are the following:

- (1) inclusion criteria that were pre-defined only in relatively vague form and could not be specifically verified,
- (2) no influence on the distribution/frequencies in which the various disorders were included,
- (3) only few connections between study management team and recruiting physicians during the course of trial (most parts of the on-site performance were done by trained study nurses),
- (4) no on-site monitoring, and
- (5) restricted possibilities only of timely supervisions of the centres by the project manager.

Most of these aspects were attributed to the rather pragmatic orientation of the trial, the organisational structure in health resorts and limited budgets. We tried to

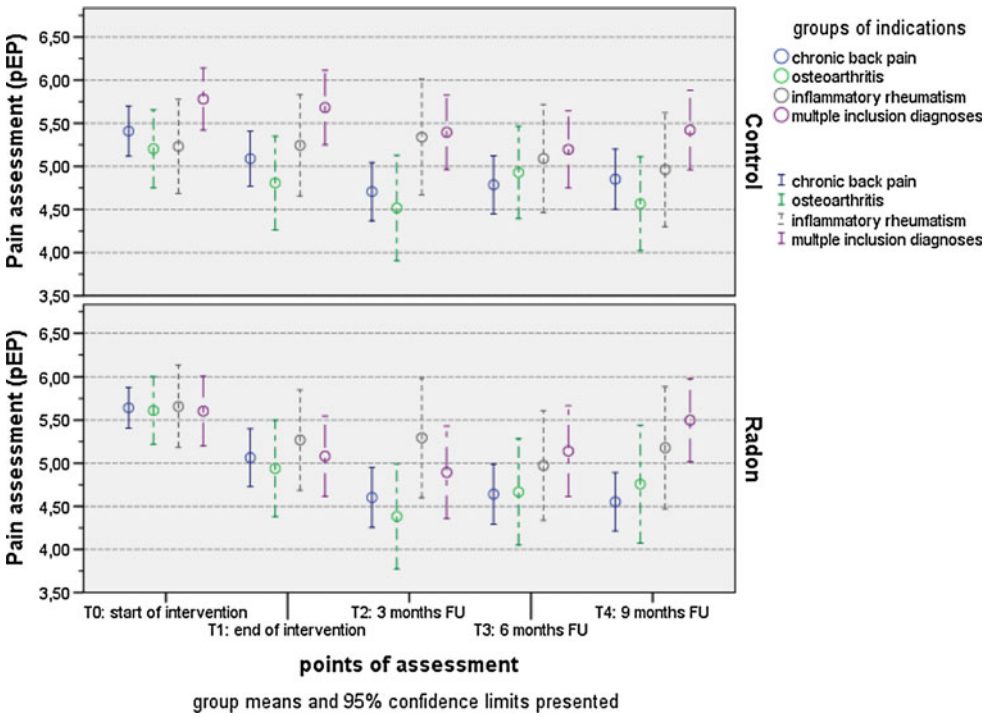

Fig. 3 Self-assessed pain (mean and 95 % confidence interval) for the indications within the treatment groups (*pEP* primary endpoint, *FU* follow-up)

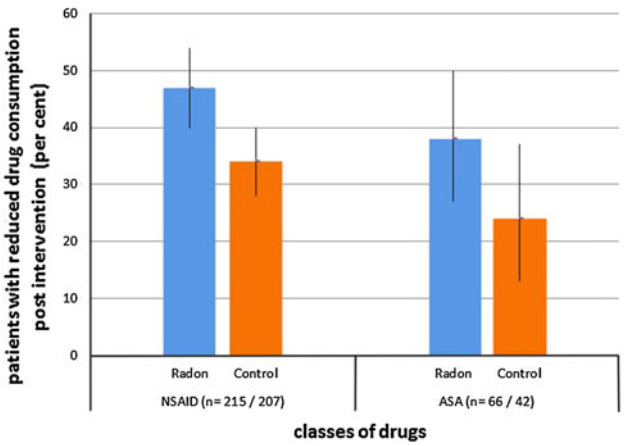

Fig. 4 Rates of reduced drug consumption after study intervention within treatment groups {with 95 % confidence interval; *NSAID* non-steroidal antirheumatic drugs including coxibe, analgesics, and/or corticosteroids, *ASA* acetylic salicylic acid or other platelets' aggregation inhibitors; $n = (n1/\ n2)$ patients with the respective medication in radon group /control group}

control potential sources of bias by suitable procedures of data management and analyses all conforming to guidelines. Due to the stratified randomisation (per centres) and the rather large sample sizes, it might be assumed that at least structural imbalances between the treatment arms were successfully avoided.

Tolerability of the radon treatment could be judged as well considered the small number of possible adverse reactions in 13 of 652 patients in more than 3,000 baths/700 gallery visits applied in total against the background of reduced medications over 9 months.

The consistency of current and former results strengthens the evidence of analgesic benefits of radon spa therapy in rheumatic disorders.

While various hints exist to explain a potentially causal relationship between radon spa therapy and pain relief in inflammatory rheumatism, nearly no biological and/or clinical rationale can be given to date regarding its potential causality to pain relief in degenerative rheumatic indications which presented the major fraction of study population.

Pain caused by OA originates in the pain receptors of synovia, periosteum, and/or capsule of joints. Complex treatment regimens usually comprise medications, physical therapy, and behavioural adaptations/changes. Pharmacologic interventions usually start with analgesics of low(er) intensity and—depending on their effectiveness—continue with stepwise upgrading to drugs of higher and highest effects, like morphine, according to common WHO-scheme of stages [39]. Under special circumstances, e.g. under high(est) physical efforts or in case of emergencies, humans are able to produce pain-relieving substances (endogenous morphine) by their own. Within some investigations [24, 40, 41], endocrinologic effects were found after radon application similar to those morphine-like analgesic effects. These may possibly present the rationale of the results observed in the OA and BP sub-populations, but further research is needed to investigate a potentially causal relationship.

Regarding inflammatory rheumatic disorders, potential explanations on modes of action regarding the inhibition of inflammation and pain relief were already summarised in [14].

Considering the meanwhile established reproducibility of positive long-term clinical outcomes with a series of radon baths, future studies should address aspects of its cost-effectiveness in more detail as started in AS [42] and the underlying biological processes regarding the mid/long-term reactions, especially in degenerative rheumatism. Proper dose-finding studies may be reasonable to combine best benefit and least risk for the patients.

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