Chapter 7

Effects of Low-Dose Radon Therapy Applied Under Hyperthermic Conditions (RnHT) on Inflammatory and Non-Inflammatory Degenerative Disease Conditions

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http://dx.doi.org/10.5772/51401

1. Introduction

Low dose radon therapy is a traditional treatment in Central and Eastern Europe typically applied to alleviate chronic pain derived from inflammatory and non-inflammatory disorders of the musculoskeletal system. Additionally it has also been reported to be effective for the treatment of chronic airway inflammation and inflammatory conditions of the skin.

Radon (^{222}Rn) is a radioactive alpha particle emitting inert gas, present in natural soil and water at several European, Japanese and American health resorts and is administered either transcutaneously by balneotherapy or per inhalationem by balneotherapy or per inhalationem by speleotherapy either at „cold" ambient temperature of 20° to 23° C (RnT) or at „hot" ambient temperatures between 37° and 41.5° C (RnHT). Speleotherapy is performed in curative caves and tunnels where radon emanation occurs due to the presence of uranium containing soil. Low dose ^{222}Rn - balneotherapy is performed in bath tubs filled with ^{222}Rn containing thermal water at a concentration typically found in the respective region but usually between 370 and 1600 Bq/L. Whereas ^{222}Rn-containing water is typically applied at 37.0° C, speleotherapeutic administration is performed either as RnT [1] or RnHT. The latter treatment regime is uniquely performed at the Gasteiner Heilstollen in Bad Gastein, Austria, which offers an average ^{222}Rn concentration of 44000 Bq/m³ in a hyperthermic atmosphere between 37.0° and 41.5° C with high humidity between 70 and 100% that facilitates a mild increase of the body's core-temperature of 0.5 - 1° Cdue to prevention of heat loss via evaporation confirmed by rectal measurement. A typical low-dose ^{222}Rn-therapy consists of

nine to ten treatment units within a period of three weeks and an effective dose of 0.05 to 2 mSv for balneotherapeutic and speleotherapeutic regimen, respectively [2]. ^{222}Rn has a half-life of 3.8 days and decays via several short-lived daughters into the beta-emitting ^{210}Plumbum with a half-life of 22.3 years. In general, radionuclide-based therapy has a long history in the management of rheumatic diseases and has been proven to alleviate pain and inflammation upon intraarticular or intravenous injection. Apart from conventional corticoid or cytostatic based therapy, radiosynoviorthesis is an alternative approach for the management of synovitis in course of chronic inflammatory arthropathies. The intraarticular injection of colloidal beta-emitters, e.g. ^{90}Yttrium, ^{186}Rhenium or ^{169}Erbium, lead to reduction of pain and joint swelling via abrogation of synovia hypertrophy by radiation-induced inhibition of the proliferative activity of synovial cells. The applied dose depends on the magnitude of the affected joint(s) and the severity of inflammation, whereas factors like intraarticular distribution of the radionuclide and thickness of the synovia dictate the absorbed dose. Therapeutic benefits in terms of pain and reduction of the inflammatory symptoms occur in 40 to 80% of the patients and manifest several months after therapy. However, numerous side effects like headache, fatigue, nausea and sometimes lymphedema, radiation-induced synovitis and periarticular necrosis due to aberrant injections have been reported [3].

Positive therapeutic effects of ^{224}Radiumchloride-injections for patients suffering from ankylosing spondylitis were reported from Koch and Reske in 1952[4], after this therapy had been abolished due to the high incidence of malignant bone tumours and leukaemia in children and young adults previously treated for tuberculosis. Until now several studies have been conducted with a reduced dose regimen of 10 weekly injections with 1 MBq each resulting in an effective dose of 2.5 Sv [5] and a cumulative bone dose of 0.6 Gy [6]. The short-lived ^{224}Radium has a half-life of 3.6 days and preferentially accumulates in the bone and in recently formed tissue calcifications when introduced into the body. In 2000 it was re-approved in Germany by the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) as a pharmaceutical product for patients suffering from ankylosing spondylitis with stage II and III spinal ossification, provided that other therapy options had either failed or been contraindicated. However, recent findings clearly demonstrated an increased incidence of leukaemia and other malignant diseases in patients that were treated between 1948 and 1975 [6]. Despite the analgesic effects elicited by ^{224}Radiumchloride-injections, the risk for malignant diseases exceeds the benefit and therefore, the committee for quality assurance of the German Society for Rheumatology no longer recommends this kind of therapy. Compared to a ^{222}Rn-speleotherapy regimen according to dosimetric calculations by Hofmann [7], the average dose to bone achieved by ^{224}Radiumchloride injection regimen is approximately a factor $3x10^5$ higher. In contrast to the bone-seeking ^{224}Radiumchlorid, inhalation of ^{222}Rn and its daughters lead to a dose distribution that predominantly affects the bronchial epithelium in the upper tracheobronchial tree. When administered balneotherapeutically, diffusion of ^{222}Rn through the skin results in a uniform dose distribution throughout the organism [7]. To the best knowledge of the authors up to date no evidence points to an increased risk for the development of malignant diseases in context with RnHT [1, 2, 8].

Hyperthermia treatment (HT) has been reported to exert analgesic effects in rheumatoid disorders, to reduce systemic levels of the pro-inflammatory cytokines TNF-alpha, IL-1beta, and IL-6 [9, 10] and to accelerate the healing of sport injuries [11]. The postulated mechanisms include increased blood perfusion of the affected tissues and relaxation of muscle tissue. Given the fact, that combined RnHT or hyperthermia alone has been reported to alleviate pain in rheumatic conditions, presently, it cannot clearly be distinguished to which extent each of the active components – ^{222}Rn and/or hyperthermia – are efficient for achieving the clinical-therapeutic benefits. According to empirical observations described below, these two agents may rather act in a synergistic manner.

Apart from clinical observations, evidence from several controlled trials, one meta-analysis and numerous clinical observational studies further substantiate the beneficial effects of intermediate up to long term pain relief and functional improvement in patients suffering from rheumatic disorders of inflammatory or degenerative etiology. From a health economic point of view, cost effective therapies in the prevention or management of rheumatic diseases are of great importance since rheumatic disorders state a relevant cost factor due to the need for long term medication, frequent hospitalizations, joint arthroplasty and loss of productivity. The dramatically increasing proportion of aged individuals further aggravates the health economic issue of rheumatic diseases since at least the prevalence of non-inflammatory, degenerative rheumatic disorders increases with progressing age [12].

The long term intake of typically employed corticosteroids and non-steroidal anti-inflammatory drugs (NSAID) for the treatment of rheumatic disorders are reported to cause severe side effects that - apart from the primary disease - result in additional medical interventions and dramatically reduce the life quality of the affected individual. Some years ago, the mortality rate caused by gastrointestinal side effects due to NSAID intake was about 2000 per year in Germany [13] and 16.500 per year in the USA [14]. Despite the additional intake of gastro-protective drugs, the ratio of NSAID-consumers suffering from gastrointestinal ulcers was 1 in 400 and the ratio of those who died was 1 in 8000 [15]. The generation of cyclooxygenase-2 inhibitors diminished the risk for gastrointestinal complications, however, the elevated risk for cardio-vascular events remained [16-18]. Taken together, from the patient´s as well as from the socio-economic point of view there is an urgent need for therapeutic strategies that allow either a reduction or discontinuation of medicament intake [19]. Combined RnHT can be regarded as a promising candidate in addressing these issues. Lind-Albrecht et al. demonstrated a long term reduction of analgesics during a 12-years follow-up in patients suffering from ankylosing spondylitis, who regularly received combined RnHT [20].

A recently published meta-analysis including 338 patients suffering from rheumatic disorders showed a superior effect of combined RnHT compared to hyperthermia therapy in terms of pain reduction [21]. Although there was no difference between the treatment groups immediately after the therapeutic regimen, the group receiving the combination of ^{222}Rn and hyperthermia showed a significantly lower pain score during the three - and six - months follow-up. Prospective, randomized studies comparing the effect of combined RnTT with either HT or no treatment were included in the meta-analysis and are described along with more recently published findings in detail below.

Franke et. al demonstrated an intermediate to long term pain reduction in patients suffering from rheumatoid arthritis during a nine month follow-up after combined RnHT. This randomized, double-blinded study included 134 patients and compared the efficacy of balneotherapeutic regimen applied at 37° C either with or without ^{222}Rn. Although both groups showed a beneficial effect immediately after therapy, the radon group predominated significantly at the three and six months follow up. Similar results were obtained concerning cut-down in NSAID and corticosteroid intake [22]. Consistent with these findings, a previous study including 60 patients with rheumatoid arthritis clearly demonstrated pain reduction and functional improvement of affected joints after a typical regimen of thermal water baths. However, patients receiving ^{222}Rn thermal water showed a significantly pronounced effect on the analyzed parameters [23].

Van Tubergen et al. investigated in course of a randomized, controlled study the efficacy of speleotherapeutically applied RnHT combined with a complex rehabilitation program including gymnastics, hydro – and sport therapy. 120 patients suffering from ankylosing spondylitis were enrolled in the study and randomized in two treatment and one control group. Whereas the control group maintained its regular physiotherapeutic program at home, the intervention groups received the complex rehabilitation program either concomitantly with hyperthermia treatment in form of sauna regimen or concomitantly with speleotherapeutic combined RnHT. Bath Ankylosing Spondylitis Functional Index (BASFI), quality of life assessment score, pain score on a visual analogue scale and duration of morning stiffness were taken together to a Pooled Index of Change (PIC) as primary endpoint. Immediately after therapy both intervention groups showed a 20 to 30% improvement in contrast to the control group that remained unaffected. In the six to nine months follow up only the ^{222}Rn group significantly prevailed [24, 25].

In line with these results, Lind-Albrecht demonstrated a significant long-term pain reduction, improved mobility of the spine and reduced drug intake of patients with ankylosing spondylitis receiving a rehabilitation program combined with speleotherapeutic RnHT compared to those, who exclusively received the rehabilitation program [26, 27].

According to two double-blinded randomized studies by Pratzel et al., an intermediate-term pain reduction could be achieved by serially applied thermal water baths with or without ^{222}Rn in patients with non-inflammatory cervical syndrome and degenerative disorders of spine or joints, respectively. Immediately after therapy both treatment groups benefitted from an elevated threshold of pressure-provoked pain in the paravertebral muscles. A sustainable and significant pain reduction lasting until the two and four months follow-up could be demonstrated only in the ^{222}Rn group [28, 29].

A recent prospective study including 222 patients suffering from non-inflammatory, degenerative rheumatoid disorders investigated the sustainability of beneficial effects achieved by serially applied ^{222}Rn containing thermal water baths. Compared to baseline levels, pain score and functional restriction of affected joints were significantly reduced up to twelve or six months, respectively. The fraction of patients with sickness absence was significantly reduced within one year after versus one year prior to therapy [30].

Although the clinical benefit of combined RnHT has been investigated, to date little is known about the underlying cellular and molecular mechanisms of action. According to findings of Reinisch et al., suppression of the oxidative burst in neutrophil granulocytes of patients suffering of ankylosing spondylitis may be at least one key element explaining the therapeutic efficacy of speleotherapeutically applied combined RnHT. Reactive oxygen species (ROS) are released from activated phagocytes in course of inflammation and play a major role in tissue destruction in rheumatoid disorders. Neutrophil granulocytes isolated from peripheral blood of patients produced significantly less superoxide anions when restimulated *ex vivo* after a regimen of ten to twelve units of combined RnHT [31].

According to a previous study by Shehata et al., pain alleviation in ankylosing spondylitis correlates to an elevation in post-treatment serum levels of the anti-inflammatory cytokine TGF-beta [32].

Apart from its role as an immune-modulator, TGF-beta1 also plays a crucial role in bone homoeostasis, particularly by acting as differentiation factor for osteoclasts and via stimulation of osteoblast and downregulation of osteoclast activity [33]. TGF-beta1 exerts its effects in concert with other cytokines and hormones by influencing the OPG/RANKL/RANK system, which is crucial in the control of osteoblast and osteoclast interplay. Receptor activator of nuclear factor κB-ligand (RANKL) is a potent stimulator of osteoclast-mediated bone resorption and promotes osteolysis. It acts via binding to receptor activator of nuclear factor-κB (RANK) on osteoclasts. Osteoprotegerin (OPG) is the functional antagonist of RANKL as it acts as a soluble RANKL decoy receptor that, upon engagement with RANKL, abrogates the interaction with RANK and consequently inhibits maturation and activation of osteoclasts and their precursors. The relative concentrations of OPG and RANKL determine the status of bone metabolism and thus, the OPG/RANKL ratio has become an important marker to assess the prevailing metabolic bone turnover situation. An increased OPG/RANKL ratio indicates an anabolic and a decreased ratio a katabolic bone metabolism state. Chronic inflammatory processes give rise to increased bone resorption, which frequently results in secondary osteoporosis, a typical complication in rheumatic diseases. Moreover, osteoporosis is further aggravated by functional and pain-related disuse bone atrophy and frequently employed glucocorticoid medication hence, predisposing the patient to a high risk of bone fracture [34]. In line with the results of Shehata et al. and the osteoimmunologic context explained above, a recently published pilot study confirmed the elevation of TGF-beta1 and demonstrated an increase of the OPG/RANKL ratio, thus indicating a shift of bone metabolism towards anabolic processes after speleotherapeutically applied RnHT [35, 36].

2. Conclusions

Numerous studies have demonstrated a sustaining beneficial effect of combined low-dose RnHT when serially applied either by speleotherapy or balneotherapy to patients suffering from inflammatory or non-inflammatory degenerative disorders of the musculo-skeletal-system. Of note, the most dominant effect is recognized several months rather than

immediately after therapy. Combined RnHT represents a cost effective method that alleviates pain and, thus, allows reducing drug intake which, in turn, may contribute to the prevention of adverse events caused by NSAIDs and glucocorticoids. As mentioned above, radionuclide-based therapy has been employed in the management of rheumatic disorders for decades. However, the poor benefit-risk ratio led to severe limitations or complete discontinuation in clinical use. RnHT poses doses to the patients which are in magnitude 10^{-5} lower in respect to the bone dose compared to ^{224}Radiumchloride-injection regimens. However, further studies are necessary to evaluate potential risks of low-dose RnHT. Although some studies implicate a beneficial effect of hyperthermia therapy for rheumatic diseases, combined RnHT turned out to be more effective than sauna or balneotherapy at an ambient temperature of 37° C lacking ^{222}Rn. As combined RnHT may also exert beneficial effects in other disease entities, further studies are necessary to prove its place among the current treatment options.

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