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Research Paper

Chronic Pain and Oxidative Stress in Knee Osteoarthritis: Role of Sulphurous Mud-Balneotherapy

Medical Science

KEYWORDS : knee osteoarthritis, Mud-balneotherapy, Oxidative Stress

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ABSTRACT

The literature demonstrated the involvement of oxidative stress in the osteoarthritis (OA) pathogenesis and the antioxidant effect of sulphurous mineral waters. Thus the objectives of the study were to investigate the impact on symptoms and quality of life and a possible antioxidant action of sulphurous mud-balneotherapy in 38 patients suffering from Knee OA admitted to Telese spa (Telese Terme, Benevento-Italy). 20 subjects (group A) did not take any NSAIDs or other drugs for gonarthrosis, 18 subjects (group B) were in treatment with ibuprofen administered orally. All patients have submitted to one cycle of mud-balneotherapy for 2 weeks by using sulphurous mineral water. Before and after the treatment in groups A and B were measured: VAS scores for pain during joint movement and the morning stiffness; Algofunctional Lequesne index; and plasma [ROMs] levels using the d-ROMs test. Sulphurous mud-balneotherapy induced a significant ($p<0.05$) reduction of the VAS score symptoms compared to basal values both in group A and in group B, with improvement of quality of life as shown by Lequesne index; moreover it was observed a significant ($p<0.05$) decrease of plasma [ROMs] levels. In conclusion this study suggests that the sulphurous mud-balneotherapy could represent an important component of the overall strategy to treat knee OA.

Introduction

Osteoarthritis (OA) is degenerative joint disease caused by an imbalance between anabolic and catabolic processes in favor of the latter (1).

Several molecules are involved in the pathogenesis of OA. Among them, Matrix MetalloProteinases (MMPs), which act on the collagen fibers and core protein of proteoglycans, have a crucial role (2). In addition, Tumor Necrosis Factor-α (TNF-α), and Interleukins (ILs), including IL-1, IL-6 and IL-17, concur to amplify cellular inflammatory response and accelerate the progression of joint tissues damage (3).

An important role in the pathogenesis of the OA is also played by oxidative stress generated by the accumulation of Reactive Oxygen Species (ROS), and by over-production of Nitric Oxide (NO) released by the inflammatory synovial cells and chondrocytes (4-6).

All the abovementioned factors contribute to produce and/or exacerbate symptoms and signs of OA, such as pain during joint movement, difficulty in the daily activities and morning stiffness (7).

The goals of OA treatment include alleviation of pain, slowing the progression of the anatomical damage and reduction of the anxiety-depressive symptoms caused by physical disability, and ultimately improving the quality of life of patients (8,9). Nowadays, available therapeutic strategies include drugs, physical rehabilitation, surgical intervention and spa (salus per aquam) therapy (10,11).

It has been demonstrated that spa therapy (12-14) is effective in reducing pain and anxiety-depressive symptoms and increasing joint functional capacity in OA, including knee OA (or gonarthrosis), which is the most common degenerative joint disease (15-17).

The spa therapy includes a number of therapeutic approaches such as bath therapy, hydropinotherapy, caves therapy and mud-balneotherapy (18).

Mud-balneotherapy is effective in reducing the number and the doses of analgesic and/or anti-inflammatory nonsteroidal anti-inflammatory drugs (NSAIDs), usually used in rheumatic diseases (12). Moreover, it has been proven to ameliorate quality of life of OA patients (13,15). Many studies have investigated on systemic and local effects of mud-balneotherapy in osteoarthritic patients in terms of mechanism of action and efficacy (6,19). It was suggested that such treatment is able to modify plasmatic levels of inflammatory and immune mediators, such as IL-1, PGE2 and TNF-a, and to activate the diencephalic–pituitary–adrenal axis by increasing the production of ACTH and endogenous opioids (such as β-endorphin) (20-24). Importantly, this seems to translate in analgesic and anti-inflammatory effects and to improve the patients mobility.

Volume : 4 | Issue : 10 | October 2015 • ISSN No 2277 - 8179

We previously demonstrated, that spa therapy with sulphurous mineral water was associated to a reduction of plasmatic levels of NO in c57 black6 mice, that spontaneously develop osteoarthritic process (6). This finding is in according with other surveys that shed in light a correlation between spa therapy and Reactive Oxygen Metabolites (ROMs) reduction (25-27).

Braga et al. (82) showed a protective effect favored by reducing properties of the sulfhydryl group contained in the sulphurous mineral water against oxidative DNA damage associated with inflammatory respiratory diseases. Moreover, we previously proposed an antioxidant effect for sulphurous mineral water administered in the form of mud-balneotherapy in subjects suffering from plaque psoriasis (29).

Up to now, data on the efficacy of spa therapy, in particular of mud-balneotherapy, for the treatment of knee OA are not exhaustive (15-17,30-32). Thus, given the possible involvement of oxidative stress in the OA pathogenesis from one hand, and the proposed antioxidant effect for sulphurous mineral waters from the other, the objectives of the present study were to investigate in patients suffering from Knee OA: a) the impact of one cycle of sulphurous mud-balneotherapy on symptoms, and quality of life and b) to evaluate a possible antioxidant action of sulphurous mud-balneotherapy.

Methods

Study design and population

A prospective longitudinal observational study was conducted on patients consecutively admitted to Telese spa (Telese Terme–Benevento, Italy). Informed consent was obtained from all participants and the research project was based on the guidelines of the Declaration of Helsinki.

The study population consisted of 38 caucasians patients (42% male and 58% female; mean age of 59±8; range age: 42-76) with a diagnosis of knee OA. The patients were divided into two groups: 20 (group A) did not take any NSAIDs or other drugs for gonarthrosis; 18 (group B) were in treatment with ibuprofen administered orally at a dose of 600 mg/die. The characteristics-descriptive statistics of both groups, A and B, are listed in Table I.

Inclusion criteria was represented by the diagnosis of knee OA in according to American College of Rheumatology guidelines (11). Exclusion criteria were as follows: acute inflammatory processes, recent surgery, intra-articular injections of steroids in the previous three months, serious venous insufficiency, active thrombophlebitis, ischemic cardiomyopathy, pacemaker implantation, uncontrolled hypertension and diabetes, cancers and pregnancy.

All patients, were subjected to one cycle of mud-balneotherapy for 2 weeks by using sulphurous mineral water (hydrogen sulfide=12.6 mg/L). The sulphurous mud-bath cycle included 12 applications of mud, one a day, applied to the knee for 15 minutes at a temperature of 44°C, followed by a cleansing shower and a bath in sulphurous mineral water at temperature of 37°-38°C for 15 minutes. Then, the patients, suitable covered, rested for 15-20 minutes lying down or reclined. This step of the treatment is called "reaction".

Before and after treatment the following parameters were evaluated:

1) ***Eventual undesirable effects,*** such as knee swelling, pain exacerbation, asthenia, skin rush and tachycardia.
2) ***The pain during joint movement and the morning stiffness*** by using 10-cm Visual Analogue Scale (VAS: 0=no pain or no morning stiffness to 10 =worst imaginable pain or morning stiffness) (33).
3) The ***impact of the spa treatment on patients quality of life*** by the algo-functional Lequesne index that provides information on intensity pain or discomfort, maximum distance walked and activities of daily living. Such index was calculated for each patient in accordance with indications reported in the literature (34). An overall score representing the sum of the scores for each test was also calculated. The overall score ranged from 0 (indicating that the patient could carry out all activities without difficulty) to 24 (a situation characterized by maximum-intensity pain, discomfort, and inability to carry out the activities of daily life).

4) Plasma concentration of reactive oxygen metabolites

Reactive Oxygen Metabolites (ROMs), primarily hydroperoxides (ROOH), is generated in cells from the attack of reactive oxygen species (ROS) on various biochemical substrates (carbohydrates, lipids, amino acids, proteins, nucleotides, etc.) (35). The ROMs are relatively more stable than ROS and thus more easily detectable and quantifiable by standard analytical procedures (35,36). Moreover, ROMs can be considered markers of early oxidative damage because of generation of two highly reactive prooxidants radicals, the alkoxyl and alkylperoxyl, which in turn promote the oxidative cascade (36). Plasma [ROMs] were measured by the d-ROMs test (Diacron, Grosseto, Italy) by using of dedicated analytical system (FREE System-Florence Spectrophotometer Slim SEAC) on peripheral capillary blood samples. It should be noted that the plasma concentration of ROMs in healthy subjects is comprised in a range of 250-300 CARR.U. (36). 1 CARR.U corresponds to 0.08 mg of H_2O_2/100mL.

Statistical analysis

The results, presented as mean ± SD, were analysed by using of Student's t-test for normally distributed data and by the Wilcoxon's signed rank test for the data with non-normal distribution. A p value ≤0.05 was considered statistically significant (37).

Results

Eventual undesirable effects

No significant undesirable events have been observed in all patients (both group A and group B) after once cycle of sulphurous mud-balneotherapy.

Pain during joint movement and morning stiffness

At baseline no differences between groups were detected (for pain joint movement: group A: 1.8±1.4 *vs* group B: 2.4±1.1; for morning stiffness: group A: 1.8±1.2 *vs* group B: 2.4±1.0). No differences between groups also after treatment (for pain joint movement: group A: 1.3±1.5 *vs* group B: 1.6±1.0; morning stiffness: group A: 1.3±1.1 *vs* group B: 1.7±0.8) were detected.

At the end of sulphurous mud-balneotherapy administered alone (group A) or in combination with drug treatment (group B), it was observed a significant reduction in pain joint movement (group A: 1.8±1.4→1.3±1.5, $p<0.05$; group B: 2.4±1.1→1.6±1.0, $p<0.01$) and in morning stiffness (group A: 1.8±1.2→1.3±1.1, $p<0.05$; group B: 2.4±1.0→1.7±0.8, $p<0,01$) when compared with the basal values (Figure 1).

Impact on quality of life

In the group A, at the end of the treatment (one cycle of sulphurous mud-balneotherapy), the analysis of the scores for each individual indicators evaluated by the Lequesne index revealed a significant reduction of *pain or discomfort* (4.0±1.9→2.3±1.6, $p<0.020$), and a significant score reduc-

tion of the *activities of daily living* (3.3±1.1→2.1±1.4,p<0,020). No significant variation in the score of *maximum distance walked* (2.0±1.7→1.7± 1.8, p>0.062) was observed (Figure 2, panel A).

In the group B, at the end of the treatment (one cycle of sulphurous mud-balneotherapy plus ibuprofen) a significant decrease of *pain or discomfort* (5.5±2.7→3.2±2.3, p<0.018), *activities of daily living* (3.8±1.4→3.0±1.7, p<0.024) and *maximum distance walked* (3.0±2.4→2.4±1.9, p<0.016) were observed (Figure 2, panel B). At baseline statistically significant change between groups A and B for *pain or discomfort subscale* was found. On the other hand, no difference between groups A and B for other sub-scales either before or after treatment were detected.

Plasma [ROMs] levels

After 2 weeks of sulphurous mud-balneotherapy, alone (group A: 346 CARR.U.±26→315 CARR.U.±54, p=0.043) or in combination with ibuprofen (group B: 343 CARR.U.±50→305 CARR.U.±42, p=0.011), a significant (p<0.05) reduction of plasma [ROMs] was observed (Table II). At baseline (group A: 346 CARR.U.±26 vs group B: 343 CARR.U.±50, p=0.849) and after treatment (group A: 315 CARR.U.±54 vs group B: 305 CARR.U.±42, p=0.630) no changes between groups A and B were found.

Discussion

The treatment of OA aims at reducing pain and disability, and preventing the progression of the cartilage degeneration, in which an important role seems to be played by the oxidative stress (4,6,9,11,35).

Evidence is accumulating in favor of the concept that salus per aquam (spa) therapy, especially mud-balneotherapy, might represent an effective adjuvant treatment of the pharmacological therapies and rehabilitation modalities, currently used for the treatment of knee OA (12,14-17,31,32). Therefore, the study on the effects of mud-balneotherapy on the knee osteoarthrosic process is deserving particular attention from researchers, even if available data in this field are still scarce.

On the basis of these considerations we investigated the efficacy of mud-balneotherapy with sulphurous mineral water in knee OA.

This study showed that just one cycle of sulphurous mud-balneotherapy (in patients of group A) induced a significant reduction in pain during joint movement and morning stiffness (assessed by VAS score), and an improvement of quality of life, assessed by subscales of the algo-functional Lequesne index.

In addition, the present study, suggested a possible antioxidant effect of sulphurous mud-balneotherapy, as demonstrated by the reduction in the plasmatic levels of ROMs (Table II).

The observed beneficial effects of sulphurous mud-balneotherapy are primarily attributable to an influence on the diencephalic–pituitary–adrenal axis with release of endorphins and cortisol, and inhibition of inflammatory mediators (IL-1, IL-6, PGE2, LTB4, TNF-α) (,20-24,38) responsible for the inflammatory-articular pain. Moreover, it is well-known that the vasodilation, locally induced by the spa mud-pack, favors the elimination of algogenic and pro-inflammatory substances with improvement of tissue trophism (15,25,38). Finally, it was also suggest that changes in the oxidative redox state, participate to the OA pathogenesis (39,40).

The addition of one cycle of sulphurous mud-balneotherapy to a pre-existing pharmacological treatment with ibuprofen (in patients of group B) revealed a significant further beneficial effects with regard to all considered symptomatic parameters (pain and morning stiffness), quality of life of the patients (assessed by Lequesne sub-scales) and plasmatic [ROMs].

This is an important survey especially when we consider that ibuprofen has been suggested to prevent carbonyl formation as well as hydrophobicity changes, which are indices of oxidative stress damage in the synovium (39). In addition, these findings, in according with other data, corroborates the hypothesis that the sulphurous mud-balneotherapy could be stimulate an anabolic response in the chondrocytes associated to an improvement of the whole body redox state (38,40).

Conclusion

This study suggests that the sulphurous mud-balneotherapy could represent an important component of the overall strategy to treat knee OA.

The decrease of plasmatic levels of ROMs observed both in patients underwent to one cycle of mud-balneotherapy and in those treated in combination with ibuprofen corroborates the hypothesis on the involvement of the [ROMs] reduction in mediating the beneficial effects of mud-balneotherapy in knee OA patients. However, further studies in a larger cohort of individuals are needed to clarify this issue.

Indeed, mud-balneotherapy could be effective both as monotherapy and in combination with NSAIDs, where it could potentiate the pharmacological action allowing a reduction of the number and the doses of the chronically used drugs and their associated adverse events.

Table I - Characteristics of the study population (groups A and B): descriptive statistics.

NUMBER OF CASES	GROUP A N=20	GROUP B N=18	Student's t test paired *p<0.05 - **p<0.01
AGE (years) Mean ±DS Median Minimum Maximum	 58±9 60 42 74	 60±8 60 44 76	NS
GENDER male (%) females (%)	 8 (40%) 12 (60%)	 8 (44%) 10 (56%)	

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Figure 1 – Mean values ±SD of total score VAS-parameters considered before and after sulphurous mud-balneotherapy alone (Group A) and in combination with drug treatment (group B).

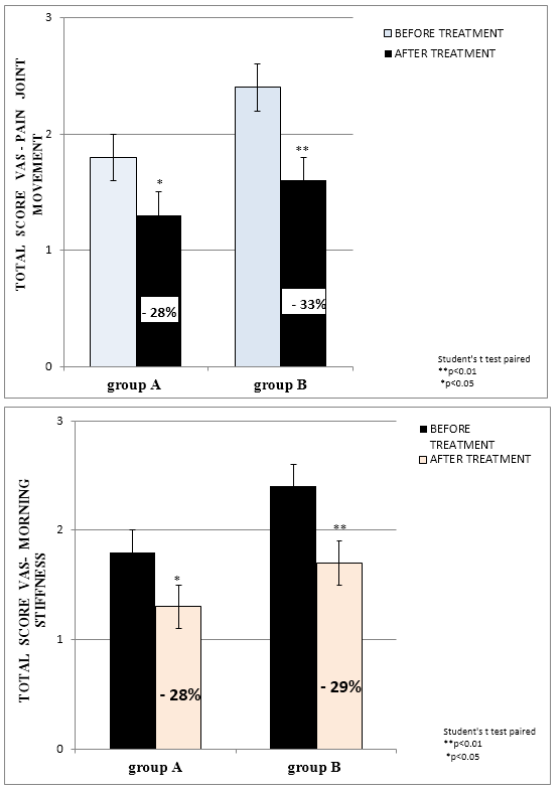

Figure 2 – Mean values ±SD measured in subscales of Lequesne's index before and after sulphurous mud-balneotherapy alone (Group A) and in combination with drug treatment (group B).

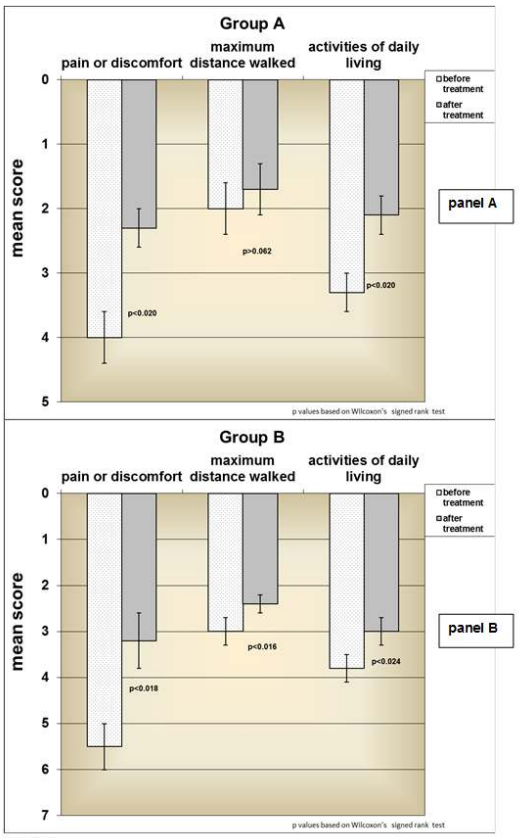

Figure 2 –

Table II - Comparison of mean values±SD of plasmatic [ROMs] levels, expressed in CARR.U., measured before and after treatment with sulphurous mud-balneotherapy: alone (group A) and in combination with ibuprofen (group B).

GROUP CONSIDERED	[ROMs] (mean±SD) before treatment	[ROMs] (mean±SD) after treatment	Student's t test paired *p<0.05 - **p<0.01
GROUP A (sulphurous mud-balneotherapy)	346 CARR.U±26	315 CARR.U±54*	p=0.043
GROUP B (ibuprofen + sulphurous mud-balneotherapy)	343 CARR.U±50	305 CARR.U±51*	p=0.011

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