IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 13, Issue 2 Ver. IV (Mar. – Apr. 2018), PP 59-63
www.iosrjournals.org

Anti-Inflammatory Effect of Serial Mud Baths in Rheumatoid Arthritis and Ankylosing Spondylitis

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Abstract: *Mud pack and bath have been used to treat musculoskeletal disorders since ancient times. However, the actual mechanisms of action of mud therapy on the inflammatory processes are complex and still not clarified. Therefore, the clinical effects of serial mud baths on the inflammatory processes in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) were investigated on the molecular level. A total of forty-one patients were recruited from an in-patient rheumatology clinic. The participants were randomized in 2 groups: the intervention group (IG: n = 21: 17 RA, 4 AS patients) underwent 9 mud bath applications in 21 days and a standardized multimodal physical therapy in an inpatient setting, whereas the control group (CG: n = 20: 16 RA, 4 AS patients) only received the multimodal physical therapy (MPT). The main outcome measures were the serum levels of interleukin(IL)-1ß, and IL-10. Secondary outcome parameters were C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), disease activity (disease activity score 28- DAS28, Bath Ankylosing Spondylitis Disease Activity Index - BASDAI), and pain (visual analog scale - VAS). The IG presented after the serial mud baths significantly decreased IL-1ß levels and significantly increased IL-10 levels, whereas the CG showed no changes of the two cytokines. CRP and ESR remained within in the normal range in both groups without significant changes. Both groups presented a significant decrease of the disease overall activity (DAS28 and BASDAI), and a significant decrease of pain (VAS), with a higher reduction in the IG. The results suggest an additive anti-inflammatory effect of serial mud baths within a multimodal physical therapy concept and could explain the beneficial effects observed in several inflammatory rheumatic diseases.*

Date of Submission: 02-04-2018 Date of acceptance: 17-04-2018

I. Introduction

The European guidelines for the treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) include non-pharmacological and pharmacological modalities [1, 2]. Mud pack and bath have been used to treat musculoskeletal disorders since ancient times [3], and favourable therapeutic effects have been demonstrated extensively in osteoarthritis [4-8]. In addition, some clinical trials have shown beneficial effects of mud application also in inflammatory rheumatic diseases such as RA [9] and AS [10]. With respect to the underlying mode of action, studies in patients with osteoarthritis have demonstrated that mud pack therapy induces reduction in circulating levels of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), interleukin-1ß (IL-1ß), tumor necrosis factor alpha (TNF-alpha), matrix metalloproteinase-3 (MMP-3), leptin, adiponectin, and can activate the diencephalic-pituitary-adrenal axis, causing increased production of ACTH and adrenocortical hormones and endogeneous opioids (cortisol, ß-endorphin, insulin-like growth factor I) [11-16]. However, the actual mechanisms of action of mud therapy on the inflammatory processes are complex and still not clarified. Therefore, the main aim of the study was to evaluate the effects of serial mud baths in patients with RA and AS on the molecular level in a controlled setting including the effect on overall disease activity and pain.

II. Material And Methods

This randomised, prospective clinical trial was carried out on in-patients of the Department of Rheumatology, Physical Medicine and Osteology, Kerckhoff-Klinik, Bad Nauheim; University of Giessen, Germany from August 2016 to August 2017. Enrolled were patients with definitive diagnosis of rheumatoid arthritis (RA, according to the American College of Rheumatology -ACR criteria) and ankylosing spondylitis (AS, modified New York criteria).

Study design: Randomised, prospective clinical study

Study Location: The study was done in the Department of Rheumatology, Physical Medicine and Osteology, Kerckhoff-Klinik, Bad Nauheim, Germany; University of Giessen

Study Duration: August 2016 to August 2017

Sample size: 41 in-patients

Sample size calculation: The study was designed as All-comes study with a descriptive nature of results.

Inclusion criteria:

1. Definitive diagnosis of RA and AS
2. low-moderate disease activity during the last 6 months
3. Aged ≥ 18 years
4. Either sex

Exclusion criteria:

1. Concomitant diseases contraindicating mud bath and multimodal physical therapy
2. Biological therapy (i.e. TNF-inhibitors).
3. Patients submitted to extensive spa therapy in the last 12 months before the study

Procedure methodology

The inpatient study protocol followed the Principles of the Declaration of Helsinki, 1964, and later amendments, and was approved by the Ethics Committee of the University of Giessen, Germany (Number 247/12). The study population was randomized (computer-generated table of random numbers) in two groups: 21 patients (12 women, 9 men, average age 55 y, 17 with RA, 4 with AS, mean duration 8 y) as an intervention group (IG), and 20 patients (10 women, 10 men, average age 57 y, 16 with RA and 4 with AS, mean disease duration 8.2 y) as a control group (CG). They all received a standardized multimodal physical therapy (physiotherapy, respiratory gymnastics, water aerobics, and occupational therapy). In the IG, 9 mud baths were applied in 21 days. Underlying pharmacological therapy was not altered during the study period. Table no 1 shows the baseline characteristics.

Table no 1: Shows demographic characteristics of the patients submitted to serial mud baths (intervention group - IG and control group - CG)

	IG (n=21)	CG (n=20)
RA/AS	17/4	16/4
Mean age in years	55	57
Sex (F/M)	12/9	10/10
Mean disease duration in years	8	8.2
Medication		
NSAIDs	n=19	n=19
Prednisolone (≤ 5mg/day)	n=15	n=14
Methotrexate (10-15 mg/week)	n=13	n=12
Sulfasalazine (2g/day)	n=4	n=4

Written informed consent was obtained from all patients prior to mud bath application. The mud bath was applied on the whole body surface with exception of the head, with a temperature of 44°C for 20 minutes. The mud used is a blend of natural clay [94%] and organic substances [6%]. For a bath application, 140 kg of fresh peat was prepared with 70 l hot water and the consistency was performed by Quentin'schen signature. The application was followed by a short lukewarm shower and a cooling phase for the patient of 30 minutes.

The outcome parameters including the molecular analyses were measured at baseline (admission to the hospital) and after completion of the serial mud baths/multimodal physical therapy (discharge). The primary outcome parameters were changes of the serum levels of interleukin(IL)-1ß and IL-10. The secondary outcome parameters were disease activity (disease activity score 28 - DAS28, Bath ankylosing spondylitis disease activity index - BASDAI), pain (by visual analog scale – VAS of the last week), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Blood samples were collected for laboratory analysis. Serum IL-1ß and IL-10 were measured using ELISA kits (R&D Systems, Quantikine®, Human IL-1ß/LI-1F2, Immunoassay, Catalog Number DLB50, SLB50, PDLB50; R&D Systems, Quantikine®, Human IL-10, Immunoassay, Catalog Number D1000B, S1000B, PD1000B), in accordance with kit manufacturer's instructions. CRP was analyzed with testkit Roche Hitachi Cobas C (Roche Diagnostics, Mannheim, Germany) and ESR by automatic determination by means of light barrier Sarstedt S2000 table device (sedimentation by Sarstedt sedivette).

Statistical analysis

Statistical analysis was performed with the Software Statistical Package for Social Sciences (SPSS program, V.11.5, SPSS, Inc., Chicago, IL, USA) for Windows. At first, the data were listed descriptively (mean ± SD), group differences were analyzed by the Mann-Whitney U -test and differences between the measuring time of the outcome parameters were detected by the Wilcoxon-test. The primary outcome parameters were significant according to Bonferroni-Holm correction. Figures are shown as mean values and SD.

III. Results

At baseline there were no significant differences between the 2 groups of the serum levels of IL-1ß, whereas the levels of IL-10 were significantly higher in the CG ($p < 0.001$). The IG presented after the serial mud baths a significantly decrease of the IL-1ß levels ($p < 0.01$) and significantly increased IL-10 levels ($p < 0.01$), whereas the CG showed no significant changes of the two cytokines (Table no 2, Figure 1). After the serial mud baths, there was no significant difference between the serum levels of IL-10 in both groups. CRP and ESR were in both groups in the normal range without significant changes (Table no 2), none of study patients presented a flare-up of the underlying disease during the study period. Both groups presented a significant decrease of the disease activity (DAS28, IG: $p < 0.01$ and CG: $p < 0.038$ and BASDAI, IG: $p < 0.01$, CG: $p < 0.01$), and a significant decrease of pain (VAS, IG and CG: $p < 0.01$; see table 2). In parallel, the NSAID medication could be finished after the study period in 10 cases of the IG (baseline 19 patients, after serial mud baths 9 patients), however, only in 2 cases of the CG.

Table no 2: Shows the results of the cytokines (IL-1ß, IL-10), disease activity (DAS28, BASDAI), and pain (VAS) in the intervention group (IG) and control group (CG)

Parameter	IG (n=21) baseline	IG (n=21) after treatment	CG (n=20) baseline	CG (n=20) after treatment	P-value Mann-Whitney U-test (group differences)	P-value Wilcoxon-test (differences between baseline and after treatment)
IL-1ß (pg/ml)	1.1 ± 0.4	0.7 ± 0.4	1.1 ± 0.3	1 ± 0.2	n.s. (baseline) 0.001 (after treatment)	0.01 (IG) n.s. (CG)
IL-10 (pg/ml)	8.5 ± 3.3	15.4 ± 10.7	18.5 ± 16.4	16 ± 15.7	0.001 (baseline) n.s. (after treatment)	0.01 (IG) n.s. (CG)
DAS28	2.7 ± 1.4	1.9 ± 1.2	5.1 ± 2.3	4.5 ± 2.1	0.001 (baseline) 0.001 (after treatment)	0.01 (IG) n.s. (CG)
BASDAI	5.9 ± 1.6	4.3 ± 1.8	5 ± 2.3	3.9 ± 2.1	n.s. (baseline) n.s. (after treatment)	0.01 (IG) 0.01 (CG)
VAS (0-10, last week)	6.8 ± 1.7	4.2 ± 2.19	5.9 ± 2.4	5.05 ± 2.3	n.s. (baseline) n.s. (after treatment)	0.01 (IG) 0.01 (CG)

Figure 1: Shows the changes in pro-inflammatory IL-1β serum levels of patients with (IG=intervention group) or without (CG=control group) serial mud bath treatment. ** $p<0.01$; ns non-significant

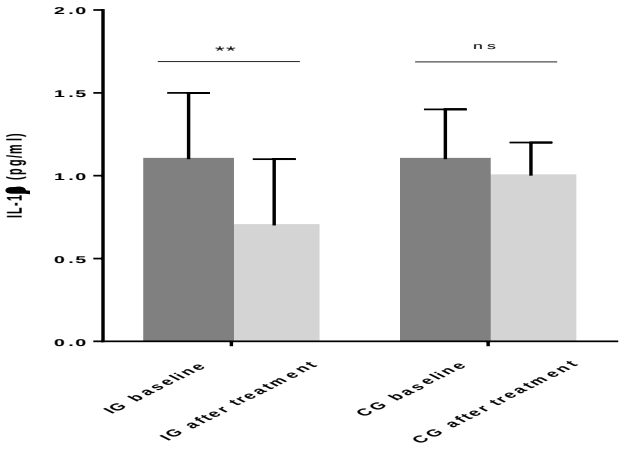
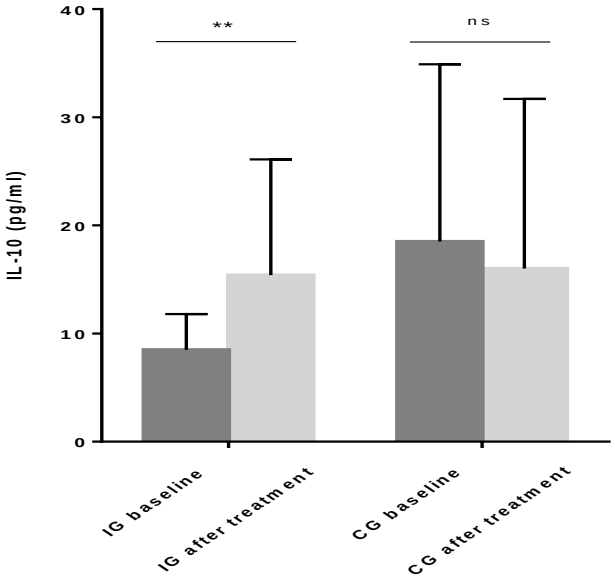


Figure 2: Shows the changes in anti-inflammatory IL-10 serum levels of patients with (IG=intervention group) or without (CG=control group) serial mud bath treatment. ** p<0.01; ns non-significant



IV. Discussion

Numerous studies addressing mud therapy have demonstrated clinical benefits and effects on inflammatory mediators (interleukins), the immune system, cenesthesic factors (endorphins), and the diencephalic-pituitary-adrenal axis, predominantly in patients with osteoarthritis [4-16]. The mechanisms of action of mud therapy are complex and not yet fully understood.

The present randomised, prospective clinical study evaluated the effect of serial mud bath application in patients with inflammatory rheumatic diseases, i.e. RA and AS. All 41 in-patients received a multimodal physical therapy, the intervention group (IG: 21 patients) had additional 9 mud baths in 21 days. After the serial mud baths the IG presented significantly decreased IL-1ß levels and significantly increased IL-10 levels, whereas the CG showed no changes. The results of IL-1ß are in agreement with other trials in animals and humans. To our knowledge, this is the first study about the anti-inflammatory effect of serial mud baths in RA and AS visualized by changes of cytokine levels, whereas the observation of the anti-inflammatory increase of IL-10 is the first documentation. Recent studies demonstrated a decrease of residual synovial inflammation and a beneficial clinical effect of mud bath therapy in patients with psoriatic arthritis treated with TNF inhibitors [17] and also in patients with enteropathic spondylitis [18] and ankylosing spondylitis [19]. Of note, it is well known that whole body hyperthermia causes immune modulating effects, and serial whole-body hyperthermia in AS results in heat-induced changes of the proinflammatory cytokine network [20].

In the present study, the mud bath applications were well tolerated, the CRP and ESR were in both groups in the normal range without significant changes and none of the patients showed a flare of the disease.

Both groups presented a significant decrease of the disease activity (DAS28 and BASDAI), and a significant decrease of pain (VAS). In addition, the reduction in the consumption of NSAIDs induced by serial mud baths after the study period is of particular importance, because of the known side effects of this class of drugs.

The benefits of the mud therapy are most likely the result of a combination of mechanical, thermal and chemical factors [21-23]. Serial heat application penetrates in deeper structures, reduces muscle and soft tissue tension and increases pain threshold in pain-sensing nerves. Furthermore, enhanced tissue perfusion due to vasodilation induced by mud bath might also promote clearance of inflammatory mediators and pain-triggering molecules, without affecting the underlying immunopathology.

Moreover, hyperthermia provokes a neuroendocrine reaction by releasing opioid mediators such as endorphins and enkephalins, leading to a pronounced analgesic effect during treatment and in the following weeks [24]. This effect is particularly important in patients with rheumatic diseases, for whom pain is the prevalent symptom. Moreover, clinical trials showed therapeutic benefits of mud bath therapy also in patients with spondyloarthritides [25-27].

The assessment of the efficacy of mud therapy in rheumatic diseases is very difficult, because a double-blind approach is not possible and even a single-blind is questionable. Therefore, limitations of the study are the

lack of a double-blind-placebo design, the small number of patients, and the short period of follow-up. However, the changes of the cytokine levels are in accordance with the positive clinical effects under serial mud bath applications.

V. Conclusion

Considering the limitations, our results induce us to hypothesize that mud baths could exert an additional beneficial effect in RA and AS, because physiotherapeutic applications provide significant measurable effects on the inflammatory process, which correlates with clinical parameters. Of note, the observation of the anti-inflammatory increase of IL-10 is the first documentation. The results thus provide further explanation for the clinically overt mechanisms of physiotherapeutical applications at the molecular level.

References

[1] Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011; 70:896-904.
[2] Schneider M, Lelgemann M, Abholz HH, et al. Interdisciplinary german guideline. Management of early rheumatoid arthritis. 3. Edition, Springer, Heidelberg, Berlin, 2011.
[3] Van Tubergen A, Van der Linden S. Brief history of spa therapy. Ann Rheum Dis 2002;61:273-5.
[4] Constant F, Callin JF, Guillemin F, et al. Effectiveness of spa therapy in chronic low back pain : a randomized clinical trial. J Rheumatol 1995;22:1315-20.
[5] Nguyen M, Revel M, Dougados M. Prolonged effects of 3 week therapy in spa resort on lumbar spine, knee and hip osteoarthritis: follow-up after 6 months. A randomised controlled trial. Br J Rheumatol 1997;36:77-81.
[6] Yurtkuran M, Yurtkuran M, Alp A, et al. Balneotherapy and tap water therapy in the treatment of knee osteoarthritis. Rheumatol Int 2006;27:19-27.
[7] Evcik D, Kavuncu V, Yeter A, et al. The efficacy of balneotherapy and mud-pack therapy in patients with knee osteoarthritis. Joint Bone Spine 2007;74:60-5.
[8] Forestier R, Desfour H, Tessier JM, et al. Spa therapy in the treatment of knee osteoarthritis: a large randomised multicenter trial. Ann Rheum Dis 2010;69:660-5.
[9] Sukenik S, Buskila D, Neumann L, et al. Sulphur bath and mud packs treatment for rheumatoid arthritis at the Dead Sea area. Ann Rheum Dis 1990;49:99-102.
[10] Tishler M, Brostovski Y, Yaron M. Effect of spa therapy in Tiberias on patients with ankylosing spondylitis. Clin Rheumatol 1995;14:21-5.
[11] Ardic F, Özgen M, Aybek H, et al. Effects of balneotherapy on serum IL-1, PGE2 and LTB4 levels in fibromyalgia patients. Rheumatol Int 2007;27:441-6.
[12] Bellometti S, Galzigna L. Serum levels of a prostaglandin and a leukotriene after termal mud pack therapy. J Investig Med 1998;46:140-5.
[13] Bellometti S, Galzigna LO, Richelmi P, et al. Both serum receptors of tumor necrosis factor are influenced by mud pack treatment in osteoarthrotic patients. Int J Tissue React 2002;24:57-64.
[14] Bellometti S, Richelmi P, Tassoni T, Bertè F. Production of matrix metalloproteinase and their inhibitors in osteoarthritic patients undergoing mud bath therapy. Int J Clin Pharmacol Res 2005;25:77-94.
[15] Fioravanti A, Cantarini L, Bacarelli MR, et al. Effects of Spa therapy on serum leptin and adiponectin levels in patients with knee osteoarthritis. Rheumatol Int 2010;31:879-82.
[16] Shimodozono M, Matsumoto S, Ninomiya K, et al. Acute effects of a single warm-water bath on serum adiponectin and leptin levels in healthy men: a pilot study. Int J Biometeorol 2012;56:933-9.
[17] Cozzi F, Raffeiner B, Beltrame V, et al. Effects of mud bath therapy in psoriatic arthritis patients treated with TNF inhibitors. Clinical evaluation and assessment of synovial inflammation by contrast-enhanced ultrasound. Joint Bone Spine 2015;82:104-8.
[18] Cozzi F, Podswiadek M, Cardinale G, et al. Mud bath treatment in spondylitis associated with inflammatory bowel disease – a pilot randomized clinical trial. Joint Bone Spine 2007;74:436-9.
[19] Ciprian L, Lo Nigro A, Ritto M, et al. The effects of Spa therapy and rehabilitation on patients with ankylosing spondylitis beeing treated with TNF inhibitors. Rheumatol Int 2013;33:241-5.
[20] Tarner IH, Müller-Ladner U, Uhlemann C, Lange U. The effects of mild whole-body hyperthermia on systemic levels of TNF-α, IL-1ß, and IL-6 in patients with ankylosing spondylitis. Clin Rheumatol 2009;28:397-402.
[21] Balogh Z, Ordogh J, Gasz A, et al. Effectiveness of balneotherapy in chronic low back pain – a randomised single-blind controlled follow-up study. Forsch Komplementarmed Klass Naturheilkd 2005;12:196-201.
[22] Cantarini L, Leo G, Giannitti C, et al. Therapeutic effect of SPA therapy and short wave therapy in knee-osteoarthritis: a randomized, single blind, controlled trial. Rheumatol 2007;27:523-9.
[23] Fioravanti A, Perpignano G, Tirri G, et al. Effects of mud bath treatment on fibromyalgia patients: a randomized clinical trial. Rheumatol Int 2007;27:1157-61.
[24] Giusti P, Cima L, Tinello A, et al. Stresshormone, freigesetzt durch Fangotherapie. ACTH- und Beta-Endorphin-Konzentrationen unter Wärmestress. Fortsch Med 1990;108:601-4.
[25] Van Tubergen A, Landewé R, van der Heijde D, et al. Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial. Arthritis Rheum 2001;45:430-8.
[26] Yurkturan M, Ay A, Karakoc Y. Improvement of the clinical outcome in ankylosing spondylitis by balneotherapy. Joint Bone Spine 2005;72:303-8.
[27] Altan L, Bingöl U, Aslan M, et al. The effect of balneotherapy on patients with ankylosing spondylitis. Scand J Rheumatol 2006;35:283-9.

Uwe Lange "Anti-Inflammatory Effect of Serial Mud Baths in Rheumatoid Arthritis and Anklosing Spondylitis."IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 13.2 (2018): 59-63.