

Is Balneotherapy Protective Against Oxidative Stress? A Pilot Study

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Abstract. *Background/Aim:* This study aimed to research the effects of Harkány healing water on oxidative stress. The study was performed in a randomized, placebo-controlled, double-blind setup. *Patients and Methods:* Twenty patients with psoriasis who underwent a 3-week-long inward balneotherapy-based rehabilitation were enrolled. Psoriasis Area and Severity Index (PASI) score and Malondialdehyde (MDA) – a marker of oxidative stress - were determined, on admission and before discharge. Patients were treated with dithranol. *Results:* The mean PASI score - determined on admission and before discharge - decreased significantly after the 3-week-long rehabilitation 8.17 vs. 3.51 ($p < 0.001$). The baseline MDA value of patients with psoriasis was significantly higher compared to controls (3.0 ± 3.5 vs. 8.4 ± 7.4) ($p = 0.018$). MDA levels of patients receiving placebo water increased significantly compared to MDA levels of patients receiving healing water ($p = 0.049$). *Conclusion:* The effectiveness of dithranol resides in the formation of reactive oxygen species. No increased oxidative stress was found in the patients treated with healing water, thus healing water seems to be protective against oxidative stress. However, further research is needed to confirm these preliminary results.

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The worldwide prevalence of psoriasis in adults varies between 0.91% and 8.5% with an incidence of 78.9/100,000 to 230/100,000 (1). Psoriasis is an incurable lifelong disease with considerable negative effects on quality of life (2). One of the most important discoveries of recent years is that patients with psoriasis have significantly increased risk of developing cardiovascular diseases, diabetes, depression, and inflammatory diseases (3-6). The pathophysiology of psoriasis is not fully understood. However, several factors are thought to play a role in the development of psoriasis. Besides genetical background and general risk factors (stress, obesity, smoking, alcohol consumption), the inordinate activation of the immune system has been identified as a key factor in the development of psoriasis (7-9). Previous studies indicated that oxidative stress plays a major role in the long-term adverse effects of psoriasis. Malondialdehyde (MDA) is one of the most widespread oxidative stress markers. Asha *et al.*, compared the MDA levels of healthy volunteers to MDA levels of patients suffering from psoriasis. Significantly higher MDA levels were found in patients with psoriasis compared to controls. Moreover, MDA levels were found to be positively correlated with the severity of psoriasis (10).

Topical agents (*e.g.*, vitamin D analogues, corticosteroids, dithranol) play a major role in psoriasis treatment. Systemic medications and natural agents (*e.g.*, peloid, UV-light, salt, healing water) are also important parts of the treatment (11, 12).

The aim of this study was to report a balneotherapy-based psoriasis rehabilitation protocol and assess its effectiveness. This study also aimed to research the effects of Harkány healing water on oxidative stress. The study was performed in a randomized, placebo-controlled, double-blind setup.

Patients and Methods

The study was a randomised (1:1 for two groups) double-blind, placebo-controlled study conducted at the Harkány Spa Hospital; Harkány, Hungary in the ISO 9001 accredited Balneology Unit from



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Table I. Clinical characteristics of the involved patients.

	Placebo group n=10	Healing water group n=10
Mean age, years	67.8±14.3	60.3±12.2
Male, n (%)	6 (60)	5 (50)
Hypertension, n (%)	5 (50)	4 (40)
Diabetes type 2, n (%)	2 (20)	1 (10)
CRP on admission	5.2±0.8	6.2±1

January 2022 to November 2022. Informed written consent to participate in the study and to publish the collected data was obtained from every patient. The study protocol was approved by the Regional Ethics Committee of University of Pécs, Pécs, Hungary (Permission No.: 7740-PTE 2019), in accordance with the Declaration of Helsinki. This trial was prospectively registered at ClinicalTrials.gov (ID: NCT04290143).

Inclusion criteria included the onset of psoriatic skin lesions, and over 18 years of age. Exclusion criteria included having received any kind of balneotherapy within 1 year before admission, receiving any kind of biological therapy, discontinuance of rehabilitation, the inability to enter and exit the treatment tub unassisted, and withdrawal of consent. Additionally, individuals diagnosed with cancer or kidney injury were also excluded.

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Patients with psoriasis were treated with Harkány healing water. Control patients were treated with placebo water in a bathtub for 30 min, twice a day, 6 days a week, during a 3-week-long inward rehabilitation. The severity and extent of psoriasis were measured by the Psoriasis Area and Severity Index (PASI). PASI score was calculated on admission and before discharge, after completing the 3-week-long rehabilitation. To rule out interobserver error, PASI score was assessed by the same dermatologist. Besides PASI score high-sensitivity C-reactive protein (hs-CRP), and MDA was measured from venous blood samples taken on admission and before discharge. Currently, there is no validated reference interval for MDA, thus 30 healthy volunteers were enrolled as MDA controls. CRP levels were determined in our University's clinical laboratory with automated analysers according to the manufacturer's protocol (Cobas 8000; Roche Diagnostics GmbH, Mannheim, Germany). MDA analysis was performed with the Lipid Peroxidation (MDA) Assay Kit (Sigma-Aldrich Co., St. Louis, MO, USA) according to the manufacturer's protocol. Samples were stored at -80°C until analysis.

Besides these objective markers of disease severity, authors aimed to find out how psoriasis affects the patients' everyday life. Questionnaires regarding the patients' complaints and overall physical wellbeing [e.g., Dermatology Life Quality Index (DLQI), 36-Item Short Form Survey (SF-36)] were filled in on admission and before discharge.

Besides healing water or placebo water, all patients received physiotherapy, electrotherapy, ultrasound therapy, UVB phototherapy, and magnet therapy. Dithranol was used 5 times a week in an ascending concentration from 0.5% to 6% according to the current dermatological status of the patient. The psoriasis rehabilitation protocol of our hospital is detailed in a previous publication (13). Details and validation of the placebo water are described in our previously published work (14).

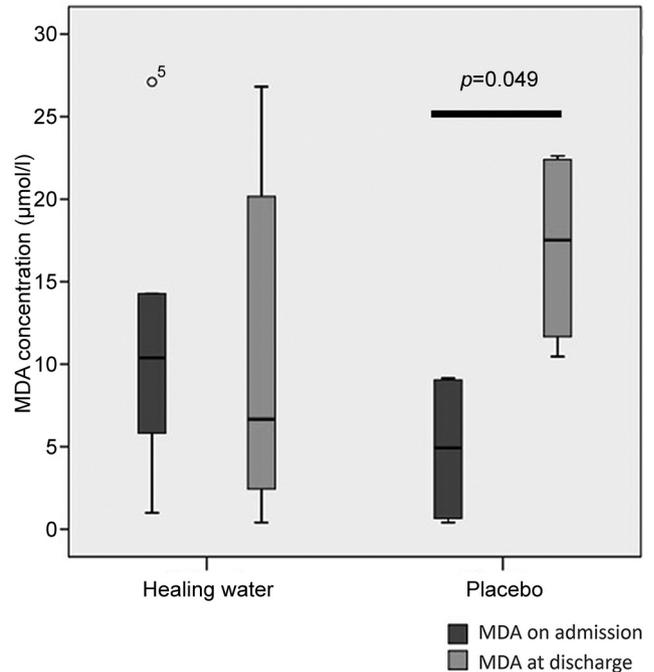


Figure 1. Malondialdehyde (MDA) concentration of patients treated with healing water and placebo water.

Statistical analysis. Statistical analysis was performed with IBM SPSS Statistics for Windows Version 22 (IBM Corp., New York, NY, USA). According to Shapiro-Wilk test, MDA values showed normal distribution, thus an error bar was used to demonstrate the results. Wilcoxon signed-rank test was used to compare the MDA values and questionnaire results. Differences between MDA values measured after admission and before discharge were compared with *t*-test. To reveal correlations, the Pearson's correlation test was used. All *p*-values less than 0.05 were considered statistically significant.

Results

A total of 112 patients with psoriasis were screened during the enrolment period. Out of the 112 patients, 22 were eligible for the study. Two patients dropped out due to infection. Finally, 20 patients completed the study. Clinical characteristics of the subjects are shown in Table I. All patients were diagnosed with psoriasis vulgaris and completed a 3-week-long inward dermatological rehabilitation. Positive family history was found in 30% of the patients. Regarding the complications of psoriasis, 30% of the patients suffered from atrophia psoriatica and 10% from arthritis psoriatica.

Patients received a combination of spa treatments during the 3-week-long inward rehabilitation. Besides placebo or healing water, all patients received dithranol, UVB phototherapy, physiotherapy, and electrotherapy. All patients' PASI score - calculated on admission and before discharge - decreased significantly after the 3-week-long rehabilitation (8.17 vs. 3.51) (*p*<0.001).

Table II. Malondialdehyde (MDA) concentration of patients treated with healing water and placebo water.

MDA levels	Placebo (n=10)	Healing water (n=10)
Admission	4.6±4.2 µmol/l	11.4±8.9 µmol/l
Discharge	19.2±6.3 µmol/l	10.5±10.8 µmol/l

Regarding the entire patient population, we found no significant difference between the CRP value measured at admission and before discharge. When examining the changes in CRP values within the two groups, we found no significant difference between the CRP values measured at admission and before discharge. The baseline MDA value of psoriatic patients was significantly higher compared to that of healthy controls (3.0 ± 3.5 vs. 8.4 ± 7.4 ; $p=0.018$). MDA levels of patients receiving placebo water increased significantly compared to MDA levels of patients receiving healing water ($p=0.049$) (Figure 1, Table II).

All patients' DLQI total score decreased significantly at discharge compared to admission ($p=0.037$). When comparing the changes of DLQI total scores of placebo patients to healing water patients, no significant differences were observed.

Regarding all patients no significant differences were found between SF-36 total score measured at discharge and SF-36 total score measured at admission. No significant differences were found between SF-36 total score measured at admission and at discharge, neither in the placebo group nor in the healing water group.

Discussion

This study demonstrated that during the 3-week-long inward balneotherapy-based rehabilitation the MDA levels of patients receiving placebo water increased significantly compared to the MDA levels of patients receiving healing water. Currently, MDA does not have a reference interval, thus the control group was comprised of healthy volunteers. MDA levels were significantly higher in psoriatic patients compared to healthy controls. MDA is a well-known oxidative stress marker, capable of representing the current oxidative status of the patients (15). Dithranol is one of the most effective and most used topical antipsoriatic agent. The effectiveness of dithranol resides in the formation of reactive oxygen species (ROS) as the cells forming the psoriatic plaque are susceptible to oxidative stress (16, 17). On the other hand, recent studies have shown that excessive oxidative stress could play a role in the development of certain diseases *e.g.*, cardiovascular diseases (18, 19), Alzheimer's disease (20), and various types of cancer (21, 22). The dithranol mediated inflammatory response was

already proven in *in vitro* and also in murine models (23, 24). According to our results, healing water seems to be capable of neutralizing the effects of oxidative stress caused by dithranol, similar to the study of Varga *et al.* (25) where healing water was shown to be protective against the oxidative stress caused by UV irradiation *in vitro*.

Regarding the ethical issues of placebo treatment, it can be stated that similar improvements were found - both in subjective (DLQI and SF-36) and objective (PASI) parameters - in both groups. These results/parameters demonstrate the appropriateness of the protocol for further studies.

In conclusion, healing water seems to be capable of reducing the harmful effects of dithranol. This pilot study was a part of a five-year long complex research program focusing on balneotherapy. According to these preliminary results the study design is feasible. Our research group will continue the patient enrolment to increase the sample size.

Conflicts of Interest

The Authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

AS: Writing draft; IP: dermatological background; NN: providing institutional background; ZA: validation; KSZ: project management, digitalization; ZHSZ: laboratory background; BSZ: laboratory background; AS: patient enrolment; AH: patient enrolment; KB: statistical analysis; BN: conceptualizing, organization, reviewing and editing manuscript.

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