

Research article

# Medicinal effects of microbubble bath on atopic eczema and psoriasis vulgaris

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**Abstract:** The incidence of atopic eczema in the population reaches generally up to 25%. Skin diseases such as Atopic eczema and Psoriasis vulgaris are a worldwide problem. Use of topical corticosteroids is the first-line treatment for atopic dermatitis flare-ups. Last individual case studies led to the hypothesis: Baths with microbubbles in tap water can significantly support the treatment of skin diseases. Microbubbles penetrate deep into the skin pores. Micro implosions occur on the pore walls, which mechanically affect nerve endings and vascular microcapillaries. In addition, due to the implosion of microbubbles, the mechanical effect leads to an increased release and flushing of substances contained in the skin pores. A total of 30 patients were selected for the study, of which 15 were included in the Study Group and 15 in the Control Group. The effects were monitored on the objectively evaluable dermatological calculators PASI, EASI, SCORAD, and DLQI Score, Quality of life, and Number and condition of foci. The project responded to the hypothesis that microbubbles in the water phase, produced by special generators, in the size range of 1-100  $\mu\text{m}$ , may in the future become a fundamental innovation in balneological treatment in the form of new treatment procedures.

**Keywords:** balneology, microbubbles, preclinical analysis, atopic eczema, psoriasis, therapeutic bath

## 1. Introduction

The incidence of atopic eczema in the population reaches up to 25%, which is attributed to environmental, dietary, and lifestyle influences. Skin diseases such as Atopic eczema and Psoriasis vulgaris are a worldwide problem. American Association of Dermatological Sciences (American Academy of Dermatology Association) reports that atopic eczema affects up to 25 percent of the world's population in varying degrees, and 2% suffer from a reduced quality of life. It is estimated that in approximately 60 percent of the population with this diagnosis, atopic eczema develops already in the first year of life, and in ninety percent of the population with this diagnosis, the disease develops before the age of 5. However, atopic eczema can also start during puberty or even later.

The preclinical study aimed to verify the hypothesis about the positive effect of a water bath with microbubbles for the supportive treatment of selected skin diseases – Psoriasis vulgaris and Atopic eczema. In addition to the results listed below, the preclinical analysis provided important data for the formulation of the assignment of follow-up clinical studies.

The therapeutic application of a microbubble water bath for skin diseases is not completely new. The original use of microbubbles mainly focused on wellness procedures,

which is still the case today. At the beginning of the 21st century, observational case studies of the application of microbubble baths appeared [7-9]. Relief was mostly achieved in individual cases of severe skin disease. However, despite the positive signal information about the effects of micro and nanobubbles on skin diseases, clinical studies have so far been lacking.

## 2. Results

### 2.1 Subjects

The selected probands had to fulfill the following criteria:

#### 2.1.1 Administrative criteria

Signature of the patient's informed consent - proband or signature of his legal representatives in the case of minor patients. Thus, consent to participate in the study was confirmed after they were fully informed about the purpose, procedures, and possible risks of the study.

#### 2.1.2 Indicative criteria for inclusion in the study

Patients with a diagnosis of Psoriasis Vulgaris with skin manifestations of psoriatic foci intended for balneological therapy.

Patients diagnosed with atopic eczema with skin manifestations of atopic eczema are intended for balneological therapy.

In patients without gender differences, in the age category 5–70 years, 5 probands were younger than 5 years.

#### 2.1.3 Contraindication criteria for exclusion from the study

Tumor diseases or after their treatment, immunodeficiency syndrome or after its treatment, other systemic diseases, acute inflammatory diseases, diabetes mellitus, and patients in the age category younger than 2 years and older than 70 years.

### 2.2 Evaluation of data obtained

The condition improved in both the Study and Control groups. The final report stated that probands with a lower initial disability score in almost all monitored indicators were included in the Control group. On the contrary, patients with greater disabilities, i.e., significantly higher initial values in the mentioned indicators, were mostly included in the Study Group. The selection procedures were always consulted with the clinical spa workplace in such cases and gradually improved. For the continuation of preclinical analysis and clinical tests, it is assumed that subgroups will be established for each evaluation calculator, which at least partially eliminates the unequal starting point, i.e., the initial health status of the patient. In general, a comparable effect of therapy for skin disease with elements of chronicity occurs mostly only after a significantly longer therapeutic effect. In the interests of the objectivity of the follow-up clinical trial, it will be necessary to establish stricter rules for deciding which treatment plan will be chosen based on the established input data. Despite the aforementioned problem of grouping, the completed investigation of 15 probands in the Study Group demonstrated a significant benefit of the microbubble bath. The significantly heavier initial severity of disability of the members of the study group, characterized by dermatological indices, must then be correctly interpreted in the context of the influence of severe disability in comparison to the effect of the normal therapeutic spa process in the Control group. There are more details in the subsequent description of the evaluation indices. Photographic documentation, reports from the initial checkup, and subsequent reports document the beneficial effect of microbubbles on skin diseases. The assessment of the number of foci at the beginning and end of the treatment stay corresponds to this finding.

### 2.2.1 PASI index

PASI (Psoriasis Area and Severity Index) and other indices evaluating probands with psoriasis (DLQI score – the quality of life, number of foci). The index PASI is the most widely used tool for measuring the severity of psoriasis. The PASI combines ratings of lesion severity and affected area into a single score ranging from 0 (no disease) to 72 (maximum disability). Purpose: to measure the severity of Psoriasis. Due to the low number of evaluated probands (two in the Control group and two in the Study group), the data obtained have significance only as data obtained by observation. All four probands improved their psoriatic condition. This number of probands only allows us to evaluate the observation of the effect of microbubble baths on the severity and extent of psoriasis. Relevant statistical results can only be derived from more significant numbers within follow-up clinical tests.

### 2.2.2 EASI index

EASI (Eczema Area and Severity Index) is a simple tool for determining the extent and severity of atopic dermatitis. However, it does not take into account dryness or peeling of the skin, it focuses only on inflammatory foci. Some sources limit its applicability to patients older than 8 years.

TABLE No. 1 COMPARISON OF GROUP EASI SCORE

EASI	Study group	Control group
Input average	16,24	10.95
Output average	13,16	7.22
% improvement	18.96	34.06

The EASI score in the Control group documents very mild initial disability at the level of an average of 10.95 disability points. On the contrary, the EASI in the Study Group shows a significantly higher initial average disability at the level of 16.24 points, which is a worse initial disability by more than 50%. The statement obtained by the experience of dermatologists is valid, according to which each EASI and similarly SCORAD evaluation point towards a more significant disability, signals a more difficult and time-consuming treatment. The value of the improvement is formally markedly higher in the Control group. The explanation is simple, in this group was included a proband whose entry rating is at an almost undetectable level of AD severity (value 1.8), in the end, an incredible improvement to 0.20. For such a case, it is necessary to interpret the possible causes of the inconsistency of EASI and the Number of foci or the exclusion of such individuals from the Control group. The most significant factor causing the mentioned inconsistency is the prevalence of a more severe condition of atopic eczema (AE) in the Study Group. Since it is methodologically at the level of preclinical analysis of the effect of microbubbles, it is possible to consciously accept the adaptation of the methodology of the division into Control and Study groups to practical circumstances. When allocating patients to both groups according to the principle of the comparable health status of the proband, including the severity of atopic eczema, the influence of the personal interest of the accompanying child patient was unfortunately also applied. The follow-up sometimes required the inclusion of the patient in the Study Group with a prospective promising treatment method precisely given his currently more difficult condition. At a higher level of AE burden, care must be taken to adhere to the treatment plan. In the 15-member Study Group, a total of six times during the treatment stay, a situation occurred that the condition after the microbubble procedure did not calm down in the usual way. According to discourses, it was

then found that in these cases the ointments were applied in the morning before the microbubble bath. Their hydrophobic effect closed the pores and made it difficult for the microbubbles to penetrate the skin.

### 2.2.3 Index Number of foci

For each proband with atopic dermatitis, the Number of foci at the initial examination and the final examination is reported.

TABLE NO. 2 COMPARISON OF THE NUMBER OF GROUP FOCI

Number of FOCI	Study group	Control group
Input average	11.93	9.80
Output average	10,13	10.93
% improvement/deterioration	15.08	-11.53

The occurrence of the Number of foci characterizes the positive effect of microbubbles on the healing process. Even with a significantly higher number of foci in the input values in the Study group, their average number decreased from 11.93 to 10.13 in this group. On the contrary, in the Control group, there was an increase in the average number of foci from 9.80 to 10.93 i.e., an increase against the entry by 11.5%, which documents the positive effect of the microbubble bath. At the same time, it is necessary to take into account the significantly higher initial total number of foci in the Study Group, 179 compared to 147 in the Control Group.

### 2.2.4 SCORAD index

As a clinical objectified tool, SCORAD assesses the extent and severity of atopic eczema – AE in atopic dermatitis. Given the nature of this disease, the fact that it is a chronically developing dermatosis that is treated symptomatically is essential. It serves as a means of objectively evaluating the severity of lesions.

TABLE No. 3 COMPARISON OF SCORAD SCORE OF GROUPS

SCORE	Study group	Control group
Input diameter	47.02	37.49
Output average	32.94	28.87
% improvement	29.94	22.99

The comparison of average SCORAD score values for the Study and Control groups shows significant differences. In general, probands assigned to the Study Group had significantly higher initial severity values than probands assigned to the Control Group. The degree of disability of each proband was evaluated according to Dermatology Department for Children, Motol University Hospital, Charles University Prague, Czech Republic [5]. This method of assessing the severity of AE impairment was derived according to A. Wollenberg, et al [4].

According to the categorization, the following are distinguished:

Severe Atopic eczema (AE): SCORAD 50 or more or persistent AE.

Moderate AE: SCORAD 25–50 or exacerbating AE (new flare-up of chronic disease that is not sufficiently healed or whose cause persists).

Mild AE: SCORAD up to 25 or transient AE Baseline, dry skin, basic treatment.

When applying this point distinction in the Study Group, there are 7 probands with found values above 50 points (or very close below 50), i.e., with an assessment of moderate to

severe disability. At the same time, there are very severe conditions reaching 77, 63, 63, and 69 in the group, which corresponds to a severe condition.

The average values of the Study group are practically on the border of a severe condition (47.02). Nevertheless, the Study Group with the application of microbubbles achieves an average percentage improvement of 29.94% against the improvement values of the control group with the application of standard treatment plans at the level of 22.99%.

#### 2.2.5 DLQI index

Quality of life index with atopic eczema DLQI (The Dermatology Life Quality Index)

TABLE No. 3 COMPARISON OF DLQI SCORE OF GROUPS

DLQI	Study group	Control group
Input diameter	23.40	20.30
Output average	15.40	14.29
% improvement	34.18	29.60

As already mentioned above, the Control group included probands with a significantly lower disability, so standard medical spa treatment puts the evaluation of the effect of microbubbles on AE at a disadvantage. The results of the Study group to which the microbubble baths were applied are more pronounced than would correspond to the current output values. The DLQI index is a questionnaire with ten questions applied to measure how much the skin problem affects the patient's personal life. It is edited in two versions - up to and after the age of 16. The improvement in this evaluation calculator despite the lower input values of the probands in the Control group shows the positive effect of the microbubble bath - see the percentage difference in both groups. The Study group improved by 34.18%, and the Control group improved by 29.60%.

### 3. Discussion

Microbubbles in the water bath are the main agent in cleaning, blood circulation, and mechanical irritation of the skin pore walls. The study was aimed at supporting the treatment of Atopic Eczema and Psoriasis Vulgaris.

We did not find a published study that investigated the clinical effect of micro or nanobubbles in a water bath on a set of probands divided into a Study Group and a Control Group. From the first cases of observation, it seems that it is possible to achieve different effects, for example, when applying different amounts of gas in the volume of water (retention, concentration). Accordingly, it is possible to hypothesize that within a certain concentration range of microbubbles, the pore-cleaning effect will be more appropriate in terms of intensity of impact with the wall of the skin pore, or width of cleaning. It seems that, for example, the concentration of microbubbles will possibly have a more positive effect at its lower level, but within a defined concentration range. Another factor that will need to be investigated is the size of the micro and nanobubbles. At the same time, the definition of microbubble size includes a range from 1 to 100 microns. Below 1 micron, these are already nanobubbles. The size of the bubbles can thus directly correlate with the depth of skin cleaning. Zeta potential, pH, or temperature affects the functionality of the entire bath in leaps and bounds, which will be reflected in the choice of organic or chemical additives in the future. The choice of such physicochemical properties of microbubbles should be adapted to the continuously monitored condition of the patient. Monitoring the patient's condition is a matter of course during the patient's stay in the medical facility. After discharge from a three or four-week stay in an inpatient treatment facility, the patient's condition slowly returns to the original worse state of health in the home environment. The solution is the use of portable microbubble generators applied in a domestic bathtub for remote monitoring of ICT status and photo documentation using a

smartphone. The doctor will be able to remotely monitor changes in the patient's health status and at the same time change available measures regarding the length of the bath and its temperature.

In the preclinical study in question, we did not notice any problems with vigilance during applications. There was no harmful effect of microbubbles in a standard tap water bath. Due to the theoretical risk of an inappropriate effect, the objective effect on the stratum corneum will have to be investigated in follow-up studies at the level of effects on biomarkers and immunomarkers. This should identify the refinement of the list of contraindicated conditions in subsequent standard clinical trials.

No manufacturer of equipment for the generation of microbubbles, which would have the possibility of regulating their physicochemical properties, has been identified in the world. [7-9]. The authors of this study, therefore, approached several manufacturers of microbubble technology for water baths to develop such devices with the ability to control the size, shape, number of bubbles, and other selected physicochemical properties.

For the continuation of preclinical analysis and clinical tests, it is assumed that subgroups will be established for each value calculator, which at least partially eliminates the unequal starting i.e., entry, and health status of the patient. In general, a comparable effect of therapy for skin disease with elements of chronicity occurs mostly only after a significantly longer therapeutic effect. In the interests of the objectivity of the follow-up clinical trial, it will be necessary to establish stricter rules for deciding which treatment plan will be chosen based on the established input data. In other words, whether the patient will be included in the project and in which group.

#### 4. Materials and Methods

The project was carried out according to the Study Plan and Study Protocol, which were discussed and approved by the Ethics Committee of the Faculty Hospital of the Faculty of Medicine of Charles University in Pilsen, Czech Republic. The project was technically secured with a bathtub-type LUSSO 180 MINIMILK+, equipped with a microbubble generator, according to the manufacturer's data, in the size of around 30-50  $\mu\text{m}$ .

Microbubbles penetrate deep into the skin pores. Micro implosions occur on the pore walls, which mechanically affect nerve endings and vascular microcapillaries. In addition, due to the implosion of microbubbles, the mechanical effect leads to an increased release and flushing of substances contained in the skin pores and thus to a cleansing and detoxifying effect and skin hydration [1]. As part of vasodilatation, the oxygen released from the microbubbles is increasingly distributed, which has an oxygen-therapeutic effect even in the place of damaged skin. This improves metabolic processes related to regeneration and healing, as well as signaling processes affecting the immune system. According to systematic research, the hypothesis of the therapeutic effect of micro and nanobubbles, which have an anti-inflammatory effect and support the healing processes in the skin structures described in [2-3], was established.

The realization of the study, data collection, and evaluation was carried out in cooperation with the Healing Spa Lazne Kynzsvart and the Balneology Research Institute. The title of the task was the pre-clinical study of the effect of microbubbles in a water bath on skin diseases of children and adult patients. A total of 30 patients were selected. 15 patients were assigned to the Study Group and 15 ones to the Control Group. For the Control group, a standard treatment plan was applied. The Study group completed an identical treatment plan plus one microbubble baths every day of the week except Sunday.

The clinical condition of the probands was evaluated using calculators for the aforementioned dermatological scores at the initial examination and after the end of treatment. Reference and randomization principle: as part of a comprehensive initial checkup, probands are selected systematically so that they meet the criteria for inclusion in the study

according to the indication criteria of the study protocol, and vice versa, so that patients who meet the contraindication criteria of the protocol are not included in the study. The principle of randomization and Placebo, the principle of double blinding was not applied.

Microbubble bath procedure used treatment with tap water containing generated microbubbles. The procedure was applied daily, except Sunday, for 20 min. in water with a temperature of 37 degrees C, with a determined volume of approx. 150 l of tap water appropriate to the body volume of the proband. The total duration of medical stay was 28 days for pediatric patients and 21 days for adult patients.

All patients were examined as standard during the initial medical checkup. Patients meeting the indication criteria were informed about the possibility of their inclusion in the study. Enrolled patients were further examined according to the study protocol. The exit checkup was carried out to the same extent as the entrance examination. The applied standard spa treatment procedures were the same for all probands in both groups as far as possible.

A Proband Status was prepared for each proband, which included, in addition to informed consent, the monitored parameters of the study: a questionnaire at the start of the spa treatment, a questionnaire at the end of the spa treatment, entry, and exit questionnaire for the dermatological index of the patient's quality of life, initial medical examination, follow-up medical examination, final/exit medical examination, a form for measuring foci of the affected skin with time-resolved photo documentation, established labeling and recording of PASI (BSA) or EASI score, SCORAD, DLQI score, Quality of life and Number and condition of foci, the record of adverse effects and side effects due to applied spa treatments.

#### *4.1 Proband status*

The status of each proband was recorded in a structured medical record as follows:

- Entrance checkup
- Personal and family anamnesis
- Current illnesses, including up-to-date treatment
- Allergic anamnesis
- Work anamnesis
- Medication used
- Report from the treating general practitioner
- Prescribed diets

Spa medical care procedures were determined identically for all probands. Their application was carried out taking into account their respective diagnoses. The structured medical record was kept in the form of an electronic record within the information system used by the workplace. Records in the information system of the workplace were kept with secure protection of personal and sensitive data under applicable laws and GDPR guidelines.

#### *4.2 Photodocumentation*

In the course of the treatment, photo documentation of the affected areas of the skin was taken. Photo documentation was taken 5 times for each proband - before the start of treatment, at weekly intervals during and after the end of treatment. Color images were taken with a 20 Mpx camera and printed on a 360-dpi color printer in A5 format. Electronic records of photo documentation are kept for each proband separately.

#### *4.3 Measurement of foci*

Measurements of damaged and healing skin foci were measured with a ruler or a flexible tape with a scale in cm. Measurements were performed during the initial checkup,

control checkup at weekly intervals, and final checkup. Measurements were performed on all areas of the affected skin, which were photo-documented, except for cases where it was practically impossible to measure due to a very complicated shape and vaguely defined area.

#### 4.4 Dermatological score evaluation record

PASI scores (Psoriasis Area and Severity Index 0–72) were determined for patients with a diagnosis of Psoriasis vulgaris during the initial and final checkups, and the obtained values for each proband were recorded in a form for measuring the foci of affected skin. The evaluation of the PASI score was performed on the Psoriasis Area Severity Index (PASI) online calculator - <http://pasi.corti.li/>. For patients diagnosed with atopic eczema, the EASI score (Eczema Area and Severity Index), SCORAD score (SCORing Atopic Dermatitis), and measurement of foci of affected skin [4,6].

The EASI calculation was performed on the calculator <http://scorad.corti.li/> was used to evaluate the SCORAD score.

#### 4.5 Biomarkers

Biomarkers have not been monitored at this stage of the preclinical study. They will be included in the clinical trial preparation phase.

### 5. Conclusions

The results of the preclinical analysis confirm the suitability of continuing research, development, and experimentation in the field of microbubble baths gradually up to the level of clinical trials of therapeutic microbubble procedures. Therefore, the conclusions of the study recommend proposing assignment topics for the methodology of diagnostic selection of probands, for the choice of suitable physicochemical properties of microbubbles (size, retention, etc.), for the choice of a suitable treatment plan according to the diagnosed groups, but with possible adjustments for each proband, for the evaluation methodology effect on a specific proband and the entire group, to a self-learning procedure for improving the effectiveness of the treatment plan based on knowledge from clinical practice using AI methods.

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