Spa Therapy for Bronchial Asthma

Studies at the Misasa Medical Center

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Bronchial asthma is usually well-controlled with bronchodilators and antiallergic medication. However, some patients cannot control asthmatic attacks without relying on oral glucocorticoids and their long-term use is associated with side effects of hypertension, diabetes, osteoporosis, and adrenal insufficiency as a result of suppressed adrenal function. These patients, who are diagnosed as having steroid-dependent intractable asthma (SDIA), represent the greatest challenge for physicians, and many attempts to wean these patients to a lower dose of corticosteroid have often been unsuccessful. In light of the prevalent use of alternative and complementary medicine in the United States, many alternative treatments have been explored except one nonpharmacologic therapy widely used in Europe and Japan—spa therapy.

There have only been a few studies conducted at the Dead Sea, Israel, for pulmonary diseases and, of those studies, most involved primarily chronic obstructive pulmonary diseases (COPD) and climatotherapy.[1,2] But the most extensive research on spa therapy for pulmonary diseases has been conducted at the Misasa Medical Center, at the Okayama University Medical School, Tottori, Japan, for more than 20 years.

Although the Japanese balneologists (spa physicians) at the Misasa Medical Center have extensive experience in treating other pulmonary diseases, this review of their research will be limited only to bronchial asthma.

At the Misasa Medical Center, spa therapy consists of swimming training in a hot spring pool for 30 minutes; 5 times per week; inhalation of 1.0 mL of iodine salt solution (KI 134 mg/L and NaCl 14.664 g/L), twice per day; and *fango* therapy. *Fango* therapy is a treatment involving mud taken from the Ningyo pass and heated to 70–80°C before being packed with cloth (40–43°C) to make compresses. For our research *fango* was applied to patients' backs for 30 minutes, 5 times per week. Patients' responses to therapy was evaluated according to the following guidelines:[3]

- Marked efficacy—Patients' asthma attacks clearly disappeared and need for glucocorticoid treatment was reduced.
- Moderate efficacy—Asthmatic attacks clearly reduced but patients still had occasional dyspnea with wheezing, or the dose of glucocorticoid could not be reduced, despite relief from symptoms
- Slight efficacy—Slight reduction in asthmatic attacks but patients had persistent dyspnea and wheezing and still required glucocorticoid medications
- No efficacy—No change in asthmatic attacks without reduction of glucocorticoid medications.

Spa efficacy was defined as having marked or moderate efficacy. Furthermore, all patients with bronchial asthma and those with SDIA were categorized according to clinical symptoms.[3] They are as follows:

- Type Ia-1— simple bronchoconstriction consisting of wheezing and dyspnea; amount of expectoration was limited to 0–49 mL per day
- Type Ia-2—same as above but with expectoration of 50–99 mL per day
- Type Ib—bronchoconstriction + hypersecretion of more than 100 mL per day
- Type II—bronchiolar obstruction.

Direct Effects of Spa Treatment

Ventilatory Functions

Spa therapy at the Misasa Medical Center began in 1982 with swimming training in a hot spring pool.[4] The responses of patients with bronchial asthma was favorable and swimming training continued until 1985.

From 1986 to 1989, spa therapy consisted of swimming training in a hot-spring pool, plus inhalation of an iodine salt solution. From 1990 to the present time, all of the Center's pulmonary patients have undergone complex spa therapy, which consists of swimming training in a hot-spring pool, inhalation of an iodine salt solution, and *fango* therapy. Although patients with bronchial asthma had a favorable response to swimming training in a hot-spring pool, this sole treatment modality was insufficient for patients with SDIA.[3]

In an attempt to understand the individual components of spa therapy and complex spa therapy better, Mitsunobu et al.[5] recruited 36 patients with bronchial asthma, mean age 56.8 (range, 21–73 years old) to undergo both individual treatments and complex spa therapy. All patients underwent individual treatment of swimming training in a hot-spring, inhalation of an iodine salt solution, and *fango* therapy. Baseline ventilatory function was measured by spirometry and compared to ventilatory function 30 minutes after patients underwent individual therapies. Likewise, baseline ventilatory function was performed before complex spa therapy and compared to the ventilatory parameters at 1 month, 2 months, and 3 months.

The results of individual therapies all revealed improvement predominantly in %MMF (maximal midexpiratory flow), %V50 (maximal flow at 50 percent of forced vital capacity), and %V25 (maximal flow at 25 percent of forced vital capacity), all indicative of small-airway improvement. However, the magnitude of changes in these parameters all differed, showing *fango* to be the most effective treatment, followed by the iodine salt solution, and swimming training in the hot-spring pool. With regard to complex spa therapy, parameters indicative of small-airway improvement were again noted, most prominently between the second and third month.

To evaluate the efficacy of complex spa therapy in relation to clinical asthma types, Tanizaki et al.[6] investigated 50 patients with bronchial asthma by observing the improvement of ventilatory function after therapy for 1–3 months. The percent increase in ventilatory function of all subjects was +3.7 percent in %FVC (forced vital capacity), +6.5 percent in FEV_1% (forced expiratory volume in 1 second/FVC), +27.2 percent in %MMF, +29.3 percent in %V50, and +24.5% in %V 25, respectively.

In relation to clinical asthma types, a lesser increase in FEV_1% and a moderate increase in %MMF, %V50, and %V25 were observed after spa therapy for patients with type Ia asthma. The highest increase in $FEV_{1.0}$% among patients of three asthmatic types, accompanied by marked improvements of %MMF, %V50, and %V25, occurred in patients with type Ib asthma. In patients with type II asthma, the improvement of %V25 was more predominant compared to the improvement ofs %MMF and %V50.

With regard to spa efficacy, a 10-year study on spa therapy and bronchial asthma[4] showed a mean efficacy of 68.2 percent ± 11.1 percent (years 1982–1985) for swimming training in the hot-spring pool; 87.5 percent ± 7.3 percent (years 1986–1989) for spa therapy consisting of swimming training and inhalation of iodine; and 94.8 percent ± 1.3 percent for complex spa therapy (years 1990–1991).

The prior study[5] had showed that complex spa therapy primarily improved the small airways. However, most of the patients with asthma in that study suffered from a decrease in FEV_1 being that this parameter is commonly associated with airway narrowing. Some of the patients also experienced a reduction in FVC.

Mitsunobu et al.[7] examined the effect of spa therapy on these two pulmonary parameters before and after spa therapy in relation to clinical asthmatic types. Thirty-six (36) patients with asthma who fulfilled the criteria of having a %FVC of <80 percent were recruited into the study; the mean age of the participants was 58.6 (range, 23–77 years old). They were divided into four different groups, according to their clinical symptoms and underwent complex spa therapy. At the conclusion of the study, %FVC increased in all four clinical groups but was only statistically significant in the type Ia-1 (P<0.001) and type Ib (P<0.05) groups. No significant changes were noted in FEV_1% among the four groups.

Bronchial Sensitivity

Many factors, such as allergy, environmental factors, and mental factors, can initiate an asthmatic attack. To evaluate bronchial sensitivity, Mitsunobu et al.[8] recruited 52 patients with asthma; their mean age was 56.8 (range, 21–72 years old). The participants underwent 1–3 months of complex spa therapy.

The study's primary endpoints were the effects of spa therapy and bronchial sensitivity in relation to clinical efficacy and age. The patients were divided evenly into two age groups: 20–59 and 60+ years of age. Bronchial sensitivity was tested with methacholine, prepared in different concentrations (49, 98, 195, 390, 781, 1563, 3125, 6250, 12500, and 25000 μg/mL) according to a method used by Chai et al.[9] The patients' Cmin (minimal threshold concentration causing a significant increase in total respiratory resistance, measured by the oscillation method) was determined[10]

With regard to spa efficacy, 21 of 26, or 80.8 percent of older patients (60+ years old) responded more favorably than younger patients (20–59 years old). Spa efficacy in younger patients was found in 19 of 26 patients or 73.1 percent. Baseline measurement before spa therapy revealed that the mean Cmin in older patients was higher (811 ± 843 μg/mL) compared to the Cmin of younger patients (353 ± 216 μg/mL).

After spa therapy, bronchial sensitivity significantly decreased in older patients by an increase in mean Cmin to 2313 ± 1961 μg/mL (P<0.02). Younger patients also had a significant increase in mean Cmin to 860 ± 610 μg/mL (P<0.01) after spa therapy. Moreover, among older patients, responders had a mean Cmin 1674 μg/mL as opposed to nonresponders with a mean Cmin of 625 μg/mL.

This study showed that bronchial sensitivity could be improved after spa therapy as documented by an increase in mean Cmin in the methacholine-challenge test in both group. However, spa efficacy was more effective in older patients and appeared to be influenced also by degree of bronchial sensitivity.

Chemical Mediators

In addition to bronchial sensitivity, release of chemical mediators such as histamine and leukotriene B_4 and C_4 , are commonly involved in both immediate and late asthmatic responses. While histamine and leukotriene C_4 have bronchoconstriction properties, leukotriene B_4 is a strong chemotactic factor that recruits leukocytes into allergic reaction sites in the airway.

Mitsunobu et al.[11] examined the effect of spa therapy on these chemical mediators in 28 patient with bronchial asthma; the mean age was 54.6 (range 22–74). Half of his recruits had SDIA. The researchers' findings revealed that spa efficacy was found in patients with low concentrations of histamine, thus suggesting that spa therapy was more favorable in patients with nonatopic asthma because those with atopic asthma have higher histamine levels as a result of their IgE-mediated allergic reactions. Furthermore, spa efficacy was found in patients with elevated levels of leukotriene B_4 and C_4, thus indicating that spa therapy was more effective in patients with greater airway inflammation.

Indirect Effects of Spa Therapy

Suppressed Adrenal Function

The earlier study by Tanizaki et al.[3] had shown that SDIA with suppressed adrenal function resulting from corticosteroids increased the subjects' serum cortisol levels after spa therapy. Kajimoto et al.[12] explored this phenomenon further by dividing 20 patients with bronchial asthma into three groups according to their baseline serum cortisol levels: group A had serum cortisol >10 μg/dL; group B had serum levels between 9.9 and 5.0 μg/dL; and group C had serum levels <5.0 μg/dL. All patients underwent complex spa therapy for 1–3 months.

The study's primary endpoint was the change in serum cortisol level before and after spa therapy. In addition, the investigators were interested in the effect of 20 minutes of bathing on serum cortisol levels for all three groups and defined positive reactivity to bathing as an increase in serum cortisol level after bathing.

Spa efficacy was found in patients with low concentrations of histamine.

Groups B and C had statistically significant increases in their serum cortisol levels at the conclusion of the study ($P<0.05$ and $P<0.01$, respectively). Only groups B and C had positive reactivity to 20 minutes of bathing. As a result, an increase ratio (the level after spa therapy minus the level before spa therapy, divided by the level before spa therapy) of serum cortisol was calculated to examine responders versus nonresponders in these two groups.

Group B, composed of 7 patients, had 4 patients with positive reactivity to 20 minutes of bathing while 5 of 7 patients in group C had positive reactivity. A total of 9 patients (4 patients from group B + 5 patients from group C) with positive reactivity had a mean increase ratio of 2.8 ± 2.9 compared to five nonresponders (3 patients from group B + 2 patients from group C) with a mean increase ratio of 0.59 ± 0.46. The difference in mean increase ratio in responders versus nonresponders was statistically significant ($P<0.01$).

The researchers concluded that serum cortisol level increased after spa therapy in patients with baseline serum cortisol levels of <10 μg/dL. Furthermore, the researchers noted that patients who have negative reactivity to 20 minutes of bathing may need spa treatment beyond 3 months to possibly increase their serum cortisol levels. But whether extended spa treatments beyond 3 months would result in increases in serum cortisol level together with spa efficacy remains unknown.

Because spa therapy produced a positive response in patients with bronchial asthma or SDIA, Mifune et al.[13] attempted to examine the serum cortisol levels in patients with SDIA in relation to patient age, clinical asthma types, and efficacy of therapy. Forty-six (46) patients with SDIA were recruited; their mean age was 50.9 (range, 23–73 years old). The participants underwent complex spa therapy for 1–3 months. All patients had been on prednisolone (mean maintenance dose was 7.0 mg per day) for more than 2 years. The subjects were were divided into 5 age groups: 20–39; 40–49; 50–59; 60–69; and 70+.

The patients in all age groups had baseline serum cortisols level of less than 10 μg/dL before spa therapy and all groups had statistically significant increases in serum cortisol levels after spa therapy except patients in the age group comprised of subjects who were 70+ (these participants had increases in serum cortisol after spa therapy but the increases were not statistically significant).

Likewise, the patients, who were categorized according to clinical symptoms of asthma, had statistically significant increases in their serum cortisol level except subjects who had type Ia-2 asthma. Thirty-seven (37) patients who responded to spa therapy had statistically significant increases in their serum cortisol levels (a twofold to fourfold increase compared to baseline) after spa therapy in contrast to nonresponders.

The researchers concluded that patients under age 49 had higher serum cortisol levels after spa therapy compared to patients who were >60 years old. In addition, responders had statistically significant higher levels of serum cortisol at the end of the study versus nonresponders. These results corroborated the earlier finding by Tanizaki et al.[3] that, even patients with SDIA whose adrenal functions have been suppressed by oral glucocorticoids for more than 2 years could still have increased serum cortisol levels after spa therapy. This study also confirmed the earlier findings by Kajimoto et al.[12] that patients with bronchial asthma whose baseline serum cortisol levels were <10 μg/dL were more likely to have increased serum cortisol levels after spa therapy, and the magnitude of the increase in serum cortisol seemed to be a good indicator whether patients would respond to spa therapy or not.

Endocrine and Autonomic Nervous Systems

Mifune et al.[14] examined the effects of spa therapy on the endocrine and autonomic nervous systems in 12 patients with bronchial asthma <65 years old (8 females and 4 males; mean age 56.1). Of these subjects, 9 patients (75.0 percent) had SDIA. All of the study patients were admitted to the Center and underwent complex spa therapy for 1–3 months.

The mean levels of serum cortisol increased from 8.6 ± 7.6 μg/dL to 10.9 ± 7.5 μg/dL after spa therapy. This difference was not significant. However, the level of serum cortisol tended to increase in all patients whose serum cortisol levels were <10μg/dL before spa therapy; 3 of these 7 patients had marked increases. The mean level of adrenocorticotropic hormone (ACTH) also increased from 21.7 ± 12.6 pg/mL to 25.9 ± 15.2 pg/mL after spa therapy; however, this was not significant. After spa therapy, 6 of 12 patients (50.0 percent) had increased ACTH levels, 3 patients (25.0 percent) ACTH levels decreased, and 3 patients (25.0 percent) had no change.

Serum concentrations of adrenalin significantly decreased from 25.3 ± 10.1 pg/mL to 14.3 ± 7.6 pg/mL after spa therapy. After spa therapy, 8 patients (66.7 percent) had decreased adrenalin levels and 3 patients (25.0%) had no change. Increase of serum adrenalin concentrations after spa therapy was found in 1 of 12 patients (8.3 percent). Serum concentrations of noradrenalin were decreased from 393 ± 268 pg/mL to 301 ± 148 pg/mL, but the difference was not statistically significant. After spa therapy 7 patients (58.3 percent) of 12 patients had a decrease in noradrenalin levels and 5 patients (41.7 percent) had increases.

Complex spa therapy had a beneficial effect on psychologic factors in patients with bronchial asthma.

Serum levels of substance P and bradykinin were observed before and after spa therapy. The mean level of substance P was not remarkably changed before and after spa therapy. In contrast, levels of bradykinin tended to increase after spa therapy; however, this was not statistically significant.

The researchers concluded that serum concentration adrenalin was decreased and this was statistically significant, and noradrenalin levels tended to decrease after spa therapy. These results suggested that increased tension of the sympathetic nervous system is suppressed by spa therapy and mental tension may also be reduced by spa therapy.

Psychologic Factors

Yokota et al.[15] evaluated the effects of complex spa therapy on psychologic factors and utilized the following three psychologic scales to measure the results of spa therapy: the Cornell Medical Index (CMI); the Self-Rating Depression Scale (SDS); and the Comprehensive Asthma Inventory (CAI). These tests were given to 25 patients with bronchial asthma (10 were male and 15 were female; mean age was 60 years old), and the results of these examinations were compared before and after spa therapy.

The CMI test revealed that the mean point of physical symptoms decreased from 32.7 ± 14.3 before spa therapy to 25.6 ± 13.3 after the therapy; respiratory symptoms decreased from 6.6 ± 3.5 before spa therapy to 5.3 ± 3.8 after the therapy; and CIJ* symptom scores, (indicating neurotic tendency) decreased from 8.5 ± 4.9 before spa therapy to 5.8 ± 4.5 after the therapy. Physical symptoms (P<0.01), respiratory system (P<0.01) and CIJ symptoms (P<0.01) were significantly reduced after spa therapy; however the reductions of psychologic symptoms were not significant.

With regard to the SDS scale, 12 of 25 patients (48 percent) scored >40 points, indicating a depressive mental state, and the number of such patients decreased from 12 to 2 after spa therapy. The mean SDS score of all patients significantly improved from 38.7 ± 8.7 to 34.2 ± 7.4 after spa therapy (P<0.01). The mean SDS score significantly decreased from 42.9 ± 7.7 to 35.4 ± 8.2 after spa therapy in patients with severe asthma (P<0.01), however the decrease by spa therapy was not statistically significant in those with moderate asthma.

Conditioning (P<0.01), suggestion (P<0.01), fear of expectation (P<0.01), frustration (P<0.01), flight into illness (P<0.01), negative attitudes about prognosis (P <0.01), and decreased motivation to engage in therapy (P <0.01) as shown on the CAI scale were significantly reduced after spa therapy, with relatively large decreases in reduction in negative attitudes and about prognosis and decreased motivation to engage in therapy. Furthermore, the CAI score, which is the average of the categories in the CAI scale, was also significantly decreased from 37.9 ± 16.0 to 28.4 ± 17.1 after spa therapy (P<0.01). In patients with severe asthma, CAI scores significantly improved from 40.9 ± 17.2 to 29.6 ±17.5 after spa therapy (P<0.05). In contrast, patients with moderate asthma did not have statistically significant improvements in their CAI scores.

These results suggested that complex spa therapy had a beneficial effect on psychologic factors in patients with bronchial asthma.

Immediate and Distant Effects

Tanizaki et al.[16] recruited 106 patients (55 females and 51 males) with a mean age of 52.2 (range, 12–80 years old) to undergo 1–3 months of spa therapy for bronchial asthma. At the end of spa treatment, patients were encouraged to continue only swimming training in a hot-water pool when returning home as maintenance therapy. Follow-up was conducted at 1 week and 1 year later, and the results were evaluated according to clinical types of asthma.

At the 1-week follow up, the positive response rates for each group were as follows: type Ia, 38 of 51 patients or 74.6 percent; type Ib, 32 of 38 patients or 84.6 percent; and type II, 15 of 17 patients or 88.3 percent.

At 1 year, 11 patients were lost to follow-up and the positive response rates were as follows: type Ia, 67.4 percent; type Ib, 62.6 percent; and type II, 70.4 percent.

Larger drops in response rates compared to the immediate effect were seen in patients with type Ib asthma (–22.0 percent) and those with type II asthma (–17.9 percent). Closer inspection of the data in the distant-effect group showed differences between groups with or without maintenance therapy. Forty-seven (47) patients with maintenance therapy had the following positive responses: type Ia, 17 of 21 patients or 81.0 percent; type Ib, 16 of 18 patients or 88.9 percent; and type II, 7 of 8 patients or 87.5 percent. Among the 48 patients without maintenance therapy, the positive response rates were as follows: type Ia, 14 of 25 or 56.0 percent; type Ib, 4 of 14 or 28.5 percent; and type II, 5 of 9 or 55.5 percent.

Furthermore, the clinical courses of patients without maintenance therapy included a disproportionately higher rate of worsening symptoms, particularly in patients with type Ib asthma (11

*The CMI consists of 18 sections (A through R). CIJ indicates sectios C, I, and J. These have questions protaining to, respectively, cardiovascular system, "fatigability," and frequency of illness.

of 14 patients or 78.6 percent) and those with type II asthma (8 of 9 patients or 88.9 percent.

Although, initially it would appear that the positive response to spa therapy was lost on follow-up at 1 year, the positive response rate remained high after stratifying the patients according to whether or not they were engaged in maintenance therapy. The study showed that positive effects of spa therapy were not restricted only to short-term benefits but extended to long-term benefits as long as 1 year, provided that maintenance therapy of swimming training in a hot-water pool was performed after spa therapy. Furthermore, patients with either type Ib of II athsma benefited the most from spa therapy and maintenance therapy but, unlike patients with type Ia asthma, they were also the most susceptible to worsening of clinical symptoms without maintenance therapy.

Benefits of Spa Therapy

Hosaki et al.[17] recruited 33 patients with SDIA, mean age 54.9 (range, 23–71 years old) to assess glucocorticoid reduction after 1–3 months of spa therapy. These patients had been treated with prednisolone (5–15 mg per day) and inhaled glucocorticoids (200–800 μg per day of beclomethasone) for more than 2 years. All patients required prednisolone to control their asthma.

The study results were analyzed in relation to clinical asthma types. All patients had baseline serum cortisol levels of <10 μg/dL and there were no statistical differences in the serum cortisol levels among the four groups. Baseline dose of prednisone differed among the four groups with the mean dose largest in patients with type II asthma (9.7 mg/day) and the smallest in patients with type Ib asthma (5.7 mg per day).

After spa therapy, all group had reductions in their prednisolone usage but the reduction was only statistically significant in patients with type Ia-2 asthma. Overall, dose reduction was achievable in 20 of 33 patients (60.6 percent). The investigators also explored the reduction of symptoms and prednisolone use among the four groups. The type Ia-2 group, consisting of 8 patients, had reductions of prednisolone use in 7 of 8 patients (87.5 percent) with 100 percent (8 of 8 patients) reduction of symptoms.

One hundred (100) percent reduction of symptoms was also achieved in patients with type Ib asthma but only 4 of 7 patients (57.1%) were able to reduce their prednisolone use. Patients with either type Ia-1 or type II asthma (of 9 patients) had a 66.7 percent reduction of symptoms (6 of 9 patients) but the reduction of prednisolone use was 5 of 9 patients with type Ia-1 asthma and 4 of 9 patients with type II asthma.

This study showed that reduction of oral glucocorticoid use was achievable with spa therapy and, even in cases, when reduction was not possible, patients still experienced reductions in symptoms. No cases of deterioration were reported in patients who were weaned from their prednisolone during spa therapy. However, this study did not have any follow-up and, as a result, questions still remain as to how long patients can remain on their wean doses of prednisolone after spa therapy and whether the reduction of prednisolone can be maintained or reduced even further if patients were to continue hot-water pool training as maintenance therapy, as reported by an earlier study by Tanizaki et al.[16]

Evidence-Based Spa Medicine

The numerous clinical trials conducted at Misasa Medical Center on spa therapy for bronchial asthma were based on numerous subgroup analyses. Many of the subgroup analyses with regard to pre– and post–spa therapy have shown the trend in favor of spa therapy, although the results did not attain statistical significance. This was most likely the result of a small sample sizes and insufficient power (Type II error-false negative).

In other words, in conducting multiple subgroup analyses by assigning patients according to clinical asthmatic types (type Ia-1, Ia-2, Ib, II), the sample sizes in each clinical type were drastically reduced and there was low power from a statistical perspective. Had more patients been enrolled in the trial, it might have been possible to obtain statistical significance.

However, when conducting studies with multiple subgroup analysis, the results need to be interpreted cautiously[18] because multiple subgroup analyses are prone to false-positive findings (Type I errors) and should be followed up with randomized controlled trial (RCTs) for confirmation.[19]

In light of evidence-based medicine, critics of spa therapy will adamantly argue against the benefits of spa therapy from a methodological perspective. Although their arguments are valid, note that, prior to the late 1990s, numerous clinical trials on spa therapy for rheumatic diseases were either uncontrolled or poorly designed randomized controlled trials whose effectiveness was only later confirmed by a few, well-designed RCTs for chronic low-back pain,[20–22] ankylosing spondylitis,[23] fibromyalgia,[24] osteoarthrits, [25] and rheumatoid arthritis.[26]

The fact that a clinical trial is uncontrolled does not necessarily negate its importance. Uncontrolled trials conducted at the Misasa Medical Center provide important insight into the possible mechanism of spa therapy for bronchial asthma and the impressive results of these trials will need to be verified with future RCTs.

Because of the difficulty in designing double-blinded RCTs for spa therapy, the benefits of spa therapy have neither been confirmed nor denied, particularly in rheumatic diseases.[27–30] Selection of an appropriate control group that meets the demands of the patients (to minimize the attrition rate) and approval from an ethical committee can be a difficult task. Even when such RCTs are conceivable, sometimes it is almost impossible to design a double-blinded study. As a result, many spa physicians have to resort to single-blinded RCTs for which the outcome assessor is blinded to the randomization.

Conclusions

Extensive research on spa therapy and bronchial asthma has been conducted at the Misasa Medical Center over the past 20 years. This nonpharmacologic therapy has been shown to be effective for treating both bronchial asthma and SDIA. What is more, spa therapy has been especially effective for treating both type Ib and type II asthma, whose clinical symptoms of hypersecretion and bronchiolar obstruction are often refractory to other drugs except oral glucocorticoid. Patients with SDIA who were on long-term corticosteroids were able to be weaned safely while undergoing spa therapy without exacerbation of the disease.

Spa therapy has direct beneficial effects on ventilatory functions, bronchial hyperresponsiveness, and chemical mediators of airway inflammation. Equally important are the therapy's indirect effects on the adrenal gland, improvement of psychologic factors, and influence on the endocrine and automatic nervous systems.

Immediate and distant effects, when combined with maintenance programs, make spa therapy a viable nonpharmacologic option even for patients who have been on long-term corticosteroids. Many issues regarding spa therapy still need further investigation, such as its cost-effectiveness and whether reduction of prednisolone can be maintained or reduced further in patients who follow maintenance programs after spa therapy.

Furthermore, the frequency of spa treatments still needs to be defined for responders. In rheumatic diseases, positive residual effects of spa therapy have been documented for as long as 9 months in trials on chronic low back-pain[22] and 40 weeks in trials involving ankylosing spondylitis.[23] As a result, most rheumatic patients require yearly spa treatment.

Despite the impressive findings in favor of spa therapy for patients with asthma, this treatment should only be used to complement drug therapy. Although used commonly at the Misasa Center, spa therapy used for a medicinal purposes remains largely unknown to the medical community in the United States and, therefore, is not recognized as the "standard of care," both from medical and medicolegal perspectives.

The cost of spa therapy is prohibitive in the United States, mainly because spa therapy often requires a 2–3 week stay at the spa in order for the treatment to be effective.

As noted in this article, patients need at least 1–3 months for spa therapy to be effective for treating bronchial asthma. Because no clinical trials have been conducted in the United States on spa medicine, both patients and American physicians do not know what spa medicine (balneology) is about and nor do they know about its potential for treating chronic illnesses.

Patients should be told to consult with their personal medical physicians regarding treatment options. As evidence-based medicine becomes the cornerstone of medical practice, more RCTs will be needed to place spa medicine on a firm methodological ground.[31] □

References

1. Kramer MR, Springer C, Berkman N, Glazer M, Bublil M, Bar-Yishay E, Godfrey S. Rehabilitation of hypoxemic patients with COPD at low altitude at the Dead Sea, the lowest place on earth. Chest 1998;113:571–575.

2. Kramer MR, Springer C, Berkman N, Bar-Yishay E, Avital A, Mandelberg A, Effron D, Godfrey S. Effect of natural oxygen enrichment at low altitude on oxygen-dependent patients with end-stage lung disease. Ann Intern Med 1994;121:658–662.

3. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Honke N. Clinical effects of complex spa therapy on patients with steroid-dependent intractable asthma (SDIA). Arerugi 1993;42(3[pt 1]):219–227.

4. Tanizaki Y, Kitani H, Mifune T, Mitsunobu F. Ten-year study on spa therapy in 329 patients with bronchial asthma. J Jpn Assoc Phys Med Balneol Climatol 1994;57:142–150.

5. Mitsunobu F, Kitani H, Okazaki M, Mifune T, Okuda H, Tanizaki Y. Clinical effects of spa therapy on bronchial asthma: 6. Comparison among three kinds of spa therapies. J Jpn Assoc Phys Med Balneol Climatol 1992;55:185–190.

6. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Okuda H, Takatori A, Ochi K, Harada H. Clinical effects of spa therapy on bronchial asthma: 2. Relationship to ventilatory function. J Jpn Assoc Phys Med Balneol Climatol 1992;55:82–86.

7. Mitsunobu F, Mifune T, Hosaki Y, Yokota S, Tanizaki Y. Improvement of forced vital capacity (FVC) by spa therapy in patients with bronchial asthma. J Jpn Assoc Phys Med Balneol Climatol 1996;59:218–224.

8. Mitsunobu F, Mifune T, Kajimoto K, Yokota S, Tanizaki Y. Improvement of bronchial sensitivity by spa therapy in patients with asthma. J Jpn Assoc Phys Med Balneol Climatol 1995;58:241–248.

9. Chai H, Farr RS, Froehlech LA, Methison DA, Melean JA, Sheffer AL, Spector SR, Townley RG. Standardization of bronchial inhalation challenge procedures. J Allergy Clin Immunol 1975;56:323–327.

10. Grimby G, Takashima T, Graham W, Mechlern P, Mead J. Frequency of flow resistance in patients with obstructive lung disease. J Clin Invest 1968;47:1455–1465.

11. Mitsunobu F, Mifune T, Hosaki Y, Ashida K, Yokota S, Tsugeno H, Tanizaki Y. Association of spa effects with generation of leukotrienes B4 and C4 by leukocytes in patients with asthma. J Jpn Assoc Phys Med Balneol Climatol 1997;60:141–148.

12. Kajimoto K, Mifune T, Mitsunobu F, Yokota S, Kitani H, Tanizaki Y. Serum cortisol levels after 20-minute bathing suggest the function of adrenocortical glands in patients with bronchial asthma. J Jpn Assoc Phys Med Balneol Climatol 1995;58:218–223.

13. Mifune T, Mitsunobu F, Hosaki Y, Yokota S, Tanizaki Y. Spa therapy and function of adrenocortical glands in patients with steroid-dependent intractable asthma (SDIA)—relationship to clinical asthma type, patient age, and clinical efficacy. J Jpn Assoc Phys Med Balneol. Climatol 1996;59:133–140.

14. Mifune T, Yokota S, Kajimoto K, Mitsunobu F, Kitani H, Tanizaki Y. Effects of spa therapy on endocrine-autonomic nerve system in patients with asthma. J Jpn Assoc Phys Med Balneol Climatol 1995;58:225–231.

15. Yokota S, Mifune T, Mitsunobu F, Hosaki Y, Ashida K, Tsugeno H, Tanizaki Y, Saitou K, Tada S, Harada M. Psychological investigation on spa therapy in patients with bronchial asthma [in Japanese]. Arerugi 1997;46:511–519.

16. Tanizaki Y, Sudo M, Kitani H, Mifune T, Okuda H, Soda M, Takahashi K, Kimura I. Clinical effects of spa therapy on patients with bronchial asthma: Comparison between immediate and distant effects of spa therapy. J Jpn Assoc Phys Med Balneol Climatol 1990;53:146–152.

17. Hosaki Y, Mifune T, Mitsunobu F, Yokota S, Tanizaki Y. Reduction of glucocorticoids by spa therapy in patients with steroid-dependent intractable asthma (SDIA). J Jpn Assoc Phys Med Balneol Climatol 1996;59: 201–208.

18. Moreira ED, Susser E. Guidelines on how to assess the validity of results presented in subgroup analysis of clinical trials. Rev Hosp Clin Fac Med São Paulo 2002;57:83–88.

19. DeMets DL, Califf RM. Lessons learned from recent cardiovascular clinical trials: Part I. Circulation 2002;106:746–751.

20. Constant F, Collin J, Guillemin F, Boulange M. Effectiveness of spa therapy in chronic low back pain: A randomized clinical trial. J Rheumatol 1995;22:1315–1320.

21. Constant F, Guillemin F, Collin J, Boulange M. Use of spa therapy to improve the quality of life of chronic low back pain patients. Med Care 1998;36:1309–1314.

22. Guillemin F, Constant F, Collin J, Boulange M. Short and long-term effect of spa therapy in chronic low back pain. Br J Rheumatol 1994;33:148–151.

23. van Tubergen A, Landewe R, et al. Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: A randomized con-

trolled trial. Arthritis Care Res 2001;45:430–438.
24. Evcik D, Kizilay B, Gokcen E. The effects of balneotherapy on fibromyalgia patients. Rheumatol Int 2002;22:56–59.
25. Nguyen M, Revel M, Dougados M. Prolonged effects of 3 week therapy in a spa resort on lumbar spine, knee and hip osteoarthritis: Follow-up after 6 months. A randomized controlled trial. Br J Rheumatol 1997;36:77–81.
26. Franke A, Reiner L, Pratzel HG, Franke T, Resch KL. Long-term efficacy of radon spa therapy in rheumatoid arthritis—a randomized, sham-controlled study and follow-up. Rheumatology (Oxford) 2000;39:894–902.
27. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Knipschild PG. Taking baths: The efficacy of balneotherapy in patients with arthritis: A systemic review. J Rheumatol 1997;24:1964–1971.
28. Verhagen A, Bierma-Zeinstra S, Cardoso J, Bie R, Boers M, Vet H. Balneotherapy for rheumatoid arthritis [Cochrane Review]. The Cochrane Library, 2003;4:CD000518
29. Brosseau L, Robinson V, Leonard G, Casimiro L, Pelland L, Wells G, Tugwell P. Efficacy of balneotherapy for rheumatoid arthritis: A meta-analysis. Phys Ther Rev 2002:7:67–87.
30. Brosseau L, Macleay L, Robinson V, Casimiro L, Pelland L, Wells G, Tugwell P, McGowan J. Efficacy of balneotherapy for osteoarthritis of the knee: A systemic review. Phys Ther Rev 2002:7:209–222.
31. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T; CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. Ann Intern Med 2001;134:663–694.

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