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Balneohydrotherapy in the treatment of chronic venous insufficiency

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Summary

Background: Physical therapy has not been evaluated much for the treatment of chronic venous insufficiency before. The question is whether balneohydrotherapy and usual care combined is superior to usual care alone.
Patients and methods: In a randomized trial comparing spa therapy versus waiting list patients were treated on an outpatient basis in a private spa center. Patients had to be between 18 and 80 years old, with chronic venous insufficiency (stage 3 or 4 according to the CEAP classification). The balneohydrotherapy group received 18 days of treatment in Aix-Les-Bains spa center continuing their usual care. The control group continued their usual care as well during the study. The balneohydrotherapy program consisted of Kneipp therapy (10 minutes), walking 10 minutes in a special mineral water pool with underwater jets at 23 °C, massage and bathing in a mineral water tub at 34 °C. The main outcome criterion was the number of patients with 20 % self assessed improvement on the Chronic Venous Insufficiency Questionnaire at three months after therapy.
Results: 192 patients were assessed for eligibility, 99 were randomized 5 retired drew back their consent and were not included in the intention to treat analysis. None were lost to follow up. After three months 32 (66 %) patients improved in the balneohydrotherapy group and 13 (28 %) in the control group. The difference between groups was significant (odd ratio 5.08 [1.94 – 13.55], relative risk reduction 2.33 [1.42 – 3.84]).There were no serious side effects.
Conclusions: Balneohydrotherapy seems to improve quality of life of patients with chronic venous insufficiency.

Key words: Chronic venous insufficiency, varicose vein, balneotherapy, spa therapy, hydro-balneotherapy

Zusammenfassung

Balneohydrotherapie in der Behandlung der chronischen Veneninsuffizienz – eine randomisierte klinische Studie
Hintergrund: Physikalische Therapie zur Behandlung der chronischen Veneninsuffizienz wurde bislang wenig untersucht. Wir sind der Frage nachgegangen, ob eine Balneohydrotherapie mit Standardbehandlung der alleinigen Standardbehandlung überlegen ist.
Patienten und Methoden: In einer randomisierten Versuchsanordnung mit Vergleich von Badetherapie und Warteliste wurden die Patienten in einer privaten Badeeinrichtung behandelt.Sie mussten zwischen 18 und 80 Jahren alt sein und eine chronische venöse Insuffizienz CEAP 3 oder 4 haben. Die Badegruppe wurde während 18 Tagen in Aix-Les-Bains behandelt und behielt dabei ihre Standardbehandlung bei. Die Therapie bestand aus einer 10 minütigen Kneipptherapie, einem 10 minütigem Gehen in einem Mineralwasserbecken mit Unterwassersprudeln bei 23 Grad, Massage und Baden in Mineralwasser bei 34 Grad. Die Kontrollgruppe führte ihre Standardtherapie durch. Hauptzielkriterium war die Anzahl der Patienten mit 20% Verbesserung im Chronic Venous Insufficiency Questionnaire drei Monate nach der Therapie.
Ergebnisse: Von 192 Patienten wurden 99 randomisiert, 5 zogen ihr Einverständnis zurück und wurden nicht in die intention to treat Analyse einbezogen. Nach drei Monaten verbesserten sich 32 (66 %) Patienten in der Balneohydrotherapie-Gruppe und 13 (28 %) in der Kontrollgruppe. Die Differenz zwischen beiden Gruppen war signifikant (odd ratio 5.08 [1.94 – 13.55], relative risk reduction 2.33 [1.42 – 3.84]. Es gab keine Nebenwirkungen.
Schlussfolgerungen: Diese Balneohydrotherapie scheint die Lebensqualität von Patienten mit chronischer venöser Insuffizienz zu verbessern.

Introduction

Lower limb chronic venous insufficiency (CVI) is a major public health problem, with which 18 million of the French population is affected. Between 11 % and 24 % of inhabitants in the industrialized countries suffer from CVI with a female preponderance [1]. Its prevalence increases with age. It was estimated that CVI sufferers were accountable for approximately 1 – 2 % of the health care budget of European countries [2].
Various treatment methods are available with good clinical results at midterm, but also with a high frequency of recurrence. Venoactive drugs, compression therapy using bandages and compression stocking are recommended [3], but the adherence to treatment is not always optimal, especially in summer. Correction of venous reflux by open surgery or endovenous procedures including ultrasound-guided foam sclerotherapy are also recommended [3]. Only little is known about the effect of physical therapy.

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Balneohydrotherapy (also called crenobalneotherapy, balneotherapy, spa therapy or crenotherapy) is a traditional therapeutic procedure in Europe, North Africa, South America, Middle East and Japan and is sometimes used for the treatment of CVI. In France, the treatment of chronic venous disorders represents 80,000 of the 500,000 patients treated each year in spa centers. Balneohydrotherapy is delivered in a three weeks course and is reimbursed by the French national health insurance system (Caisse Nationale d'Assurance Maladie). It combines many procedures using mineral water; wandering in the pool restores the muscle pump, and the hydrostatic pressure decreases the edema, underwater massages and Kneipp technique (alternate hot and cold showers) stimulate the cutaneous vasomotor response and underwater exercises improve the aggravating locomotor factors (knee, ankle ankylosis, etc.).
This study evaluates the effect of balneohydrotherapy on the quality of life in patients with CVI.

Patients and methods

Patients were recruited locally so that they could attend the spa center on a daily basis. Announcements for the recruitment were performed mainly by advertisements in the regional press and also by posters in pharmacies and the waiting room of the specialists [5]. They referred to treatment for CVI, but did not specify the spa therapy.
Inclusion criteria were: patients 18 to 80 years old and diagnosed with CVI stage 3 or 4 according to the CEAP classification regardless of etiology [4]. Patients were included if they accepted to participate in a 3 week treatment in the spa center and to be followed-up for 6 months.
Exclusion criteria were: pregnant women, contra-indication for the spa treatment (chronic infectious diseases, cancer, heart failure, serious liver or kidney disease, open leg ulcer, psychiatric disorders, immune deficiency, phlebitis, erysipelas or history of erysipelas); planned surgery in the next 3 months, spa treatment in the previous 6 months, and professional involvement in the spa center.
All patients were evaluated by the same practitioner at the beginning of the trial and during the follow-up. This independent practitioner was a senior specialist for CVI, who had no connection with the spa center. The study took place in Aix-Les-Bains spa center (Thermes Nationaux d'Aix-Les-Bains) which is the third most important spa center in France, delivering service to 30,000 patients/year.
All participants signed an informed consent form.
At the beginning of treatment, patients were advised to continue their usual medications and to use compression therapy. A booklet with advice on lifestyle was also delivered. There where no specific requirements for the usual care.
Treatment was prescribed by the spa doctors working in private outpatient clinics. Patients were examined 3 times; just prior to the Commencement of treatment, in the middle of the 3 week period and at the end of the treatment. During the consultations, adherence to the treatment schedule was controlled and side effects were recorded.
The treatment group received 18 days of balneohydrotherapy in three weeks. The treatment comprised 4 different spa techniques daily: Kneipp therapy, walking the pool, underwater massage and a bath in a tub. After termination of the daily programme, patients would rest 20 minutes in the Trendelenburg position. Kneipp therapy is an alternating warm (28 °C) and cold (14 °C) shower on the legs of 10 minutes duration. The walking pool is 60 cm deep with an underwater shower jet at 23 °C and patients walking in it for 10 minutes without stopping. Underwater massage is performed under a 38 °C shower by a senior physiotherapist, beginning at the feet and gradually proceding to the thighs, lasting 10 minutes. The bath tub contains a underwater shower at 30 °C, which also works from the feet and gradually to the thighs over a period of 20 minutes. For each treatment modality, mineral water alone was used as it is an obligation for French spa centers. All interventions were standardized by timers. Adherence to each technique was supervised during each session as is the practice for all patients treated in the spa center. These modalities are defined for all the spa centers in France by negotiation with the health insurance system.
After admission to the programme, patients were sent to one of the spa practitioners. They were examined at the beginning, in the middle and at the end of the treatment period, as is customary in France. Body weight, heart frequency and blood pressure were systematically measured.
The same balneohydrotherapy program was proposed to the control group at the end of the study period (three months later).
The hypothesis was that after three months balneohydrotherapy would be superior to being on a waiting list for patients with CVI, as measured by self-assessment questionnaires. These were completed by the patients without the presence of the examining physician, and after the consultation in order to limit his influence on the answers.
Primary outcome was a 20 % improvement in quality of life after three months. Quality of life was measured by a French validated version of the Chronic Venous Insufficiency Questionnaire (CIVIQ 2) [6].
Secondary outcomes were based on the Rutherford severity score, CIVIQ2, change in associated treat-

ment, patient acceptable symptom state (PASS), opinion of patient and practitioner, side effects.

Rutherford severity score is a clinical evaluation of disease severity taking into account 10 attributes: pain, varicose veins, venous edema, skin pigmentation, and adherence to compressive therapy, inflammation, induration, number, size and duration of active ulcer. Each attribute is scored from 0 (minimum) to 2 (maximum). [7]

CIVIQ yields a disease-specific QOL (quality of life) score for patients with CVI. The total score is derived from 20 questions (items) that represent four QOL dimensions (of 3 – 9 items each): bodily pain, physical, social and psychological functioning. The possible scores for each item are as follows: 1, negative; 2, weak; 3, moderate; 4, strong; 5, severe. The total scores can therefore vary from 20 (no symptoms) to 100 (worse possible condition).

PASS is measured by asking the patient if he/she feels he/she is in an acceptable clinical condition in terms of his/her venous insufficiency. The opinion of the patient and the practitioner is determined on a 5 point Likert's scale (very aggravated, aggravated, unchanged, improved and very improved). Drug consumption is estimated for the last 3 days prior to the evaluation. Surgery, hospitalization for venous insufficiency and adherence to compression therapy were also evaluated.

On the basis of the only published study [8] and previous unpublished studies in our spa center, we estimated that 50 % of patient in the treatment group and 30 % of patients in the control group would have a 20 % clinical improvement. The alpha risk was chosen at 5 % and the beta risk at 20 % (for an 80 % statistical power). The number of patients to include, calculated by the Casagrande and Picke methods was 72 patients per group (totally 144 patients).

A block randomization was generated by one of the authors (RF). It was carried out with block sizes of 6, 8 and 10 patients with a random order which was determined by dice rolls. Every block comprised 50 % treatment and 50 % control, respectively. Concealed allocation was performed by the same author who was not in contact with the participants of the study. Assignment was given by telephone to the examining physician (JMM) who informed the patients.

Blinding was not possible to achieve for patients, as is the case in most non-pharmacological trials [9]. It was also difficult to achieve for the examining physician because he was informing the patients about the assignment. He was blinded to the previous answers of the patients. Blinding was not possible for the spa physicians because they were prescribing the treatment and collecting the side effects. It was not possible for the care providers since the spa center only treats patients with rheumatic diseases and treatments modalities are different. Blinding could only be realized by the statistician. The first author (RF) carried out the randomization; he performed the data entry, the data monitoring and froze the database. Then he masked the group assignment with a code. Statistical analysis was performed by the third author (AF) who was unaware of the treatment group.

Statistical analysis

Statistical analysis was performed as planned in the protocol accepted by the ethics committee. It was based on an intention to treat method. Categorical variables were expressed as frequency and percentage, continuous variables as mean and standard deviation (SD). The main endpoint was tested using an uncorrected χ^2 test. Risk ratios were reported with 95 % confidence interval (CI), and effect size with 95 % CI.

Secondary qualitative endpoints were analyzed using the same principles. For between-group comparisons at the first and third month the Mann-Whitney test was used. Two-sided p values less than 0.05 were considered statistically significant for the main criteria. Since we performed 10 statistical tests for the secondary criteria,

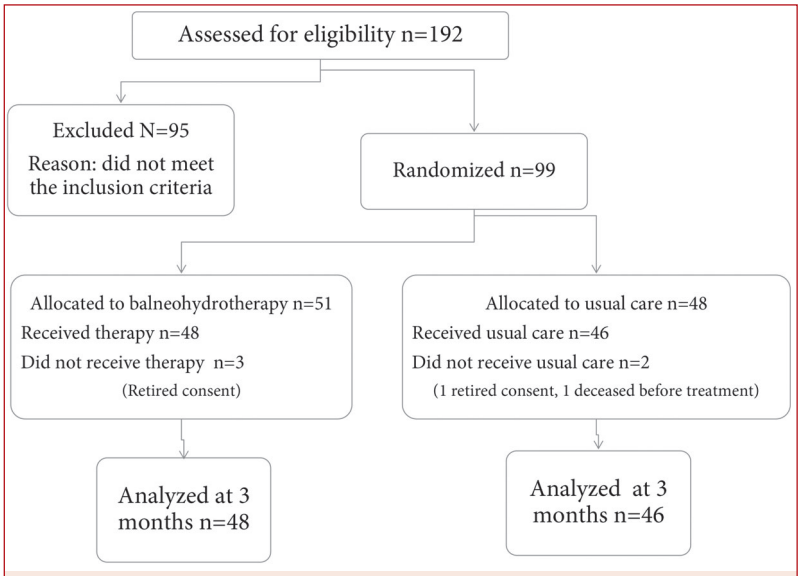

Figure 1: Flow diagram

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Table I: Baseline characteristics

	Control (n = 46)	Balneohydro-therapy (n = 48)
Sex F/M	36/10	45/3
Age (years) mean/SD	60 ± 13	58 ± 13
Venoactive drug intake (n)	9	9
Usage of compression stockings (n)	26	30
History of spa treatment for veins(n)	7	7
History of spa treatment for rheumatism(n)	17	18
History of surgery for veins (n)	27	28
Previous erysipelas (n)	1	2
Deviations in protocol (n)	1	4
CIVIC quality of life score (mean/SD)	57.2 +/–15.8	55.5 +/–14.2
Rutherford severity score (mean/SD)	8.78 +/–3.1	9.10 +/–2.5

CIVIC: Chronic Venous Insufficiency Questionnaire. (n): number of patients

the Bonferroni correction indicated that a difference was significant for a p value below 0.005. Analyses were performed using XLSTAT version 2011.02.07 (Addinsoft, Inc., USA). Effect size (ES) was calculated by dividing mean of N differences by standard deviation of value at baseline. [10]

The trial protocol passed favorably the regional ethics committee (Comité de Protection des Personnes Sud Est III) in June 2010 and Afssaps agreement (Agence Française de sécurité sanitaire des produits de santé) in 12/04/2010. The study was registered under ClinicalTrials.gov Identifier: NCT01956318. Study coordination (GB), monitoring visits (GB), data management (RF), data entry from patient questionnaires (RF), and data analysis AF) were performed by members of the Aix-Les-Bains Research Center.

Results

Patients were recruited in the period from July 2010 to February 2012. The last patient was evaluated in May 2012. 99 patients were randomized and 94 were analyzed for the main criteria (Figure 1). The two groups were similar at baseline (Table I).

Primary outcome

The number of patients in each group with 20 % improvement in CIVIQ2 is shown in Table II. The difference is significant for the main judgment criteria at the third month, odds ratio is 5.08 [1.94 – 13.55], relative risk reduction is 2.33 [1.42 – 3.84], (Chi^2: 0.00019).

Secondary outcome

There is also a significant difference at 3 weeks, at the end of the treatment. At the third week odds ratio is 7.92 [2.77 – 2.40], relative risk reduction is 3.22 [1.66 – 6.12] (Chi^2: 0.0000084). Secondary outcomes are reported in Table III: There is a greater improvement in quality of life CIVIQ (ES: 0.18 vs. 1.07), the Rutherford scale (ES: 0.03 vs. 1.31), the opinion of patient and the opinion of the examining physician following the study for the balneohydrotherapy group. The CEAP classification is reported in table IV; there is no difference between groups.

We didn't observe any serious side effect in either groups. One patient in the control group died of diffuse bleeding before starting the treatment, one case of superficial thrombosis occurred in the balneohydrotherapy group (considered as a failure of treatment). One erysipela was seen in the control group in the third week and one in the treatment group in the third month.

Table II: Number of patients with 20 % improvement on CIVIC

	Control	Balneohydro-therapy
Number of patients at third week	n = 46	n = 48
Chi^2: .0000084		
No improvement	38 (82 %)	18 (37 %)
Improvement	8 (18 %)	30 (63 %)
Number of patients at third month	n = 46	n = 48
Chi^2: .00019		
No improvement	33 (72 %)	16 (33 %)
Improvement	13 (28 %)	32 (66 %)

Discussion

This study shows that balneohydrotherapy plus usual care may provide a significant improvement of the quality of life of patients when compared

to usual care alone and this treatment was well tolerated.

Beside the quality of life, patients also have an improvement in their clinical status (Rutherford severity score), opinion of physician and opinion of patient, but not in the CEAP classification that summarizes the important results of clinical examination.

One of the strengths of our study lies in the choice of the primary endpoint. We believe it is relevant for the patient. We note that it is supported by the patient's and the practitioner's opinions. The choice of a qualitative criterion is considered likely to cancel the placebo effect [11] and also the effect of the lack of assessment blinding [12] for diseases with mainly functional symptoms such as CVI. Maybe a three month follow up is too short for three weeks of treatment. We had chosen this period to limit the lost to follow up and also for the ethical reason that the control group was not offered any additional treatment. It does not mean that the treatment effect cannot last longer.

The selection procedure recruited nearly 50 % of the patients that were examined, this offered a good chance to have a representative population of patients with CVI. This important point is not usually observed (and sometimes not reported) in other studies. Previous studies on balneotherapy are sometimes unclear regarding the population in which recruitment was made. It is well known that in pharmacologic trials patients that are included in the study are not always representative of the population to which treatment will be offered (less than 5 % in a study of antidepressants). [13]

Due to the inability to obtain a blinding of patients, it is also difficult to obtain a true blinding of the examining physician and caregivers and it may overestimate the treatment effect. We chose to use a self-completed questionnaire, filled out in the absence

Table III: Secondary outcome criteria after balneohydrotherapy and usual care

	Control	Balneohydrotherapy	P value
Quality of life (CIVIC) (mean/SD)			
Inclusion	57,3 +/–15.8	55,5 +/–14.2	,560
Third week	54,8 +/–13.8	40,8 +/–12.9	<,0001
Third month	54,7 +/–14.8	40,3 +/–15.1	<,0001
Rutherford scale (mean/SD)			
Inclusion	8,8 +/–3.1	9,1+/–2.6	,331
Third week	8,9 +/–3.5	6,3 +/–3.0	<,0001
Third month	8,7 +/–2.9	5,7 +/–3.0	<,0001
Number of improved patients (self-assessment)			
Third week OR = 68.25 [15.55 – 342.79], RR = 9.41 [3.68 – 24.07]			,00001
No improvement	42	6	
Improvement	4	39	
Third month OR = 20.89 [3.98 – 136.32], RR = 7.55 [1.99 – 28 – 71]			p = ,00001
No improvement	44	23	
Improvement	2	25	
Number of improved patient (opinion of practitioner)			
Third week OR=48.03 [12.40 – 205.52], RR = 7.86 [3.41 – 18.13]			p < 00001
No improvement	41	7	
Improvement	5	41	
Third month OR = 17.33 [4.30 – 81.23], RR = 6.44 [2.18 – 19.07]			p = ,00001
No improvement	44	22	
Improvement	2	26	
Number of patients taking venoactive drugs			
Third week	1/46	0/48	
Third month	0/46	1/48	
Number of patients using compression stockings			
Third week	6/46	7/48	
Third month	7/46	11/48	
Number of patients applying to a consultation for CVI			
Third week	3/46	0/46	
Third month	1/46	0/46	
Number of patients having surgery			
Third week	0/46	0/48	
Third month	1/46	0/48	
Number of patients suffering from recently developed erysipelas			
Third week	1/46	0/46	
Third month	0/46	1/46	

CEAP: Clinical severity, Etiology or cause, Anatomy, Pathophysiology. CIVIC: Chronic Venous Insufficiency Questionnaire. CVI: chronic venous insufficiency

Table IV: Development of CEAP classification during the study

	Baseline		Third week		Third month	
	κ^2: 1	p: 0.37	κ^2: 4.99	p: 0.17	κ^2: 7.9	p: 0.04
CEAP	C	HB	C	HB	C	HB
2	0	0	1	2	1	3
3	30	28	30	29	29	28
4	16	16	15	11	16	10
5	0	3	0	3	0	3

CEAP: clinical, etiology, anatomic pathophysiology. C: control. HB balneohydrotherapy

of the medical examiner, in order to preserve the independence of the patients. The medical examiner is an independent doctor who never had activity in connection with the spas, so as to achieve maximum objectivity in the assessment of patients. The lack of blinding of patients is known to promote the "placebo" effect. In this study, this effect is minimized by utilization of the same follow-up method for both groups [14] and the use of a qualitative endpoint as we mentioned before. It remains, however, that the lack of blinding of patients could overestimate the treatment effect. [15] The severity of the recruitment criteria led us to interrupt it at 99 while 174 patients were expected in the protocol. On the other hand, the improvement of patients in the treatment group had been higher than the estimations we made to calculate the number of subjects needed. It was sufficient to observe a significant difference between the groups. Waiting list method may overestimate the difference between groups by deception bias in the control group. It should be noted that this bias was probably of limited influence in our study since the control group improved, although insignificantly, while it remained stable [16] or worse [8] in previous studies using similar methodology.

We observed that the proportion of patients using compression therapy was high at the beginning and low during follow up. We think that it did not influence the results since the proportion of patients remained similar in both groups. We gave the same questionnaires at the entry and during the follow up. It is possible that the patients might have understood the question about compression in a different way for each evaluation. Maybe, they answered "if they had ever used compression?" at first questioning, and "if they have used a contention recently?" for the follow up. There is a possible lack of observance in the treatment. Unfortunately, we didn't evaluate observance but it was systematically collected by the supervisors of the spa center, as is usually done for all the patients treated. For the ordinary patients, observance rate in the spa center is 95 to 100 % (personal data). If it had been the case for our study, this would have underestimated the treatment effect.

Two similar studies have already been published in the same field by Carpentier et al. [8, 17] . In the first one, the primary endpoint was a measure of malleolar chromametry which has the advantage of being an objective measurement, but its clinical relevance to the patient is not known. The study compared a spa group and therapeutic education with a waiting list of patients who continued their usual treatment in the expectation of a cure at the end of the study, as in our work. It showed a significant improvement for the treatment group. Other endpoints were the same as those of our tests and improved with the same proportions. The number of patients is slightly higher in our study (99 vs. 63) and CIVIQ scale goes from 52.5 to 47 at the 3rd month in comparison to 55.5 to 40.3 in our study. On the other hand this study combined spa treatments and therapeutic education sessions that probably reinforced the effect of thermal treatment. The second is a large randomized trial also comparing balneotherapy plus patient education with waiting list patients[16]. The main criterion was not statistically different (incidence of ulcers), but the clinical improvement of CIVIC decreased from 38 to 33 at six months. The clinical status of the patients was more severe at the entry (CEAP 4 to 5 as opposed to 3 to 5 in our study). The control group had balneotherapy plus education one year later which might have caused a deception bias and overestimation of treatment effect regarding continuous subjective criteria [11]. Previous studies have been published on Kneipp therapy [18] and balneokinesis [19], but they did not choose a main criterion and did not perform intent-to-treat (ITT) analysis.

Conclusions

With some methodological limitations, this study shows an improvement of clinical status and quality of life of patients with CVI treated with balneohydrotherapy when compared with usual care and treatment and is well tolerated. Balneohydrotherapy can be proposed as a treatment option for patients with CVI, especially for those who have difficulties with the adherence to compression stockings or those for whom there is no surgical solution.

Conflicts of interest

Funding: Thermes Nationaux d'Aix-Les-Bains, France. There are no conflicts of interest existing for: Romain Forestier, Alain Francon, Fatma Begüm Erol, and Jean-Marc Mollard. The following conflicts of interest exist for Gisèle Briancon: she is an employee of Valvital, our sponsor for the study. She did no modify the article but she helped to report the implementation of the spa treatment and she organized the trial.

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