Balneotherapy for chronic venous insufficiency

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[Intervention Protocol]

Balneotherapy for chronic venous insufficiency

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To asses the effects and safety of balneotherapy for the treatment of patients with chronic venous insufficiency (CVI).

BACKGROUND

See Appendix 1 for a glossary of terms.

Description of the condition

Chronic venous insufficiency (CVI) occurs when the normal transport of superficial or deep venous blood is disturbed, causing venous hypertension and haemodynamic disturbances. This resultant inability to maintain pressure and flow to the heart in the venous system is largely responsible for the symptoms of the disease. This health condition is defined by several signs, with varicose veins the most common, and venous ulcers the most severe. Oedema, venous eczema, hyperpigmentation of the ankle skin, atrophie blanche, and lipodermatosclerosis may also be seen (Bergan 2006; Perrin 2016). It is thought that valve reflux plays a role in the aetiology of CVI, with chronic endothelial inflammation and subsequent localised dysfunction reducing the synthesis of anti-inflammatory agents, and potentially increasing the expression of pro-inflammatory molecules and cytokines, which also contribute to the disease (Beebe-Dimmer 2005; Castro-Ferreira 2018; Lee 2016). In CVI, the increase in ambulatory venous hypertension, with subsequent activation of endothelial cells, extravasation of macromolecules and erythrocytes, leukocyte diapedesis, tissue oedema, and chronic inflammatory changes, may result in oedema, hyperpigmentation, lipodermatosclerosis, eczema, or venous ulcers (Gloviczki 2011).

CVI is progressive, and has a high prevalence in the economically active population, but its impact on the quality of life of an affected individual is poorly understood (Rossi 2015). Prevalence of varicose veins in the UK has been reported to be between 20% and 40% in adults (Carroll 2013). The prevalence of venous ulcers in the general population is between 1% to 1.5%, rising to 5% in people over 80 years old. Venous ulcers can be extremely long-lasting, with about 20% of ulcers failing to heal after two years, and 8% failing to heal after five years (Carroll 2013). Nicolaides 2014 reported a prevalence of varicose veins between 25% and 33% in women, and between 10% and 20% in men. The preva-

lence of more severe stages of CVI, such as edema and cutaneous alterations, ranged from 3% to 11% (Nicolaides 2014).

The most commonly used classification in CVI is called CEAP, which was adopted worldwide to facilitate communication on CVI, and serve as a basis for a scientific analysis of the alternatives for treating the disease. It is based on clinical manifestations (C), aetiological factors (E), anatomical distribution (A), and pathophysiological findings (P), or CEAP. This classification assists in the systematic approach and orientation in the daily clinical investigation of the patients, as a system of ordered documentation, and basis for decisions regarding the appropriate treatment (Eklöf 2004).

There are a wide variety of management options or therapies for CVI, ranging from surgery and medication, to compression and physical therapies.

Traditional CVI treatments include varicose vein surgery, liquid sclerotherapy, and intravenous ablation (laser, radiofrequency, or foam sclerotherapy). Surgical removal is a common procedure for the problem, but has been associated with neuropathy, scarring, infection, bruising, deep venous thrombosis, pain, and prolonged postoperative recovery. Liquid sclerotherapy is considered faster but less effective than the conventional surgical option. Because they are minimally invasive, ablative techniques are increasingly used, and offer potential benefits, such as reduced complications, faster recovery, and fewer physical limitations, with lower recurrence rates, compared to conventional surgical techniques (Carroll 2013).

Medical treatments for the management of CVI include phlebotonic or venoactive drugs (e.g. flavanoids, such as horse chestnut, rutosides, and hesperidin (Gloviczki 2011; Martinez-Zapata 2016; Pittler 2012)).

Compression therapy and physical therapy can improve blood flow by increasing tissue pressure and improved local lymphatic drainage. This decreases venous hypertension, with an improvement in inflammation and stasis (Wong 2012). There are several different types of vascular compression therapy for use in CVI, ranging from simple wraps with uniform compression to graduated elastic stockings, which can be knee or thigh length (Konschake 2016; Motykie 1999).

Physical therapy is aimed at restoring the function of the calf muscle pump and improving health-related quality of life, and offers a useful adjunct treatment (Carpentier 2009). Reduced mobility of the ankle and decreased function of the calf muscle pump are associated with the progressive severity of CVI. The aim of these therapies is to obtain a persistent increase in the efficacy of the mechanisms facilitating venous return (Caggiati 2018). Structured fitness to improve limb muscle strength and ankle mobility may improve venous haemodynamics, mobility, and well-being by improving muscle pump function (Padberg 2004). The strengthening of the lower limb muscles may lead to beneficial changes in venous haemodynamics, allowing the reduction of blood flow, reduction of functional venous volume, residual volume fraction, and increased blood ejection fraction (Silva 2010).

Adherence to physical and compression therapy is not always good, especially in the summer (Gloviczki 2011). These techniques are considered successful, but the recurrence rates are high, ranging from 21% to 67% in compression therapy, which suggests factors beyond patient education in non-use (Raju 2007).

Physical therapies have not been mentioned in recent guidelines on CVI. However, there is increasing evidence of the role of these modalities in preventing disease progression and in optimising the results of surgical and pharmacological treatments (Caggiati 2018).

Description of the intervention

Treatments involving water (balneotherapy) have been used for centuries and are widely used today (Blain 2016). In patients with severe diseases, such as rheumatoid arthritis and osteoarthritis, balneotherapy helps improve physical function and pain relief (Verhagen 2007; Verhagen 2015).

Bathing in natural mineral or thermal waters appears to have positive effects related to specific properties of immersion in water, which are due to hydrostatic pressure, osmotic pressure, and temperature (Caggiati 2018). The effects of balneotherapy are based on both the chemical and physical properties of the agents (Gutenbrunner 2010). The aim of balneotherapy in CVI patients is to improve range of joint motion, relieve muscle spasm, and maintain or improve functional mobility (Carpentier 2014; Gutenbrunner 2010).

In some countries, balneotherapy is a popular way of treating CVI, but its efficacy has not yet been fully evaluated (Angoules 2014). For example, in France, more than 60,000 patients are treated annually in this way (Carpentier 2009). The term balneotherapy is classically used to mean bathing in thermal or mineral waters, and differs from hydrotherapy in some contexts. However, since the beginning of the 20th century, both terms have been accepted for all forms of water treatment (Johnson 1990; Verhagen 2007). Balneotherapy is also defined as the use of natural mineral waters, gases, and peloids (natural organic-mineral products formed in the course of geological processes (Pasek 2010)). Equivalent terms are hydrotherapy and crenobalneotherapy (Forestier 2014). The substances used for balneotherapy are medical mineral waters (hypothermal (< 35°C), isothermal (35°C to 36°C), and hyperthermal (> 36°C)), medical peloids (including peat, fango (of volcanic origin), mud (from sea, lakes or river beds)), clay, and natural gases (CO_2, H_2S, and radon (Gutenbrunner 2010)). Treatment is based on specific properties of the mineral water, such as hydrostatic pressure, osmotic pressure and water temperature.

Traditionally, the treatment is delivered as a three-week course in a spa resort specializing in the treatment of CVI patients. Treatment regimens usually consist of four balneotherapy sessions per day, six days a week, for three weeks. The types of balneotherapy sessions are chosen by spa physicians for each patient, according to

his or her needs and capabilities, and combines active and intensive balneotherapy, using mineral waters with a dedicated patient education program (Carpentier 2009).

In the literature, different researchers use different types of balneotherapy; there is no consensus on a rigid session therapy protocol or treatment sequence.

For example, a complete balneotherapy treatment may include one or more of the following regimens (Blain 2016; Carpentier 2009):

- whirlpool bath with automatic air and water massage;
- controlled walking in semi-deep water (to increase mobility and balance of joints, walking on a carpet of small air bubbles to stimulate proprioception and microcirculation, walking against water flow to increase the venous return by pump calf muscles);
- balance therapy, using an irregular sloping surface (promoting stimulation of the plantar arch and venous pump, relaxation of the ankles, and improvement of limb physical perception, with improvement of venous pumping);
- bath with strong underwater massaging jets;
- massage by physiotherapist under a light spray shower;
- simple bath;
- massage by physiotherapist with limbs underwater;
- application of thermal mud;
- gymnastics in deep water.

How the intervention might work

Balneotherapy combines many procedures using mineral water; movement within the pool aims to restore muscle pump action, and the hydrostatic pressure may decrease the oedema. Underwater massages and Kneipp technique (alternate hot and cold showers) stimulate the cutaneous vasomotor response, and underwater exercises may benefit aggravating locomotor factors, including knee or ankle ankyloses (Forestier 2014).

Hydrostatic pressure acts on the tissues and exerts a compression of blood vessels, which may aid in venous return and reduction of oedema and pain (Becker 2009; Forestier 2014). Heat and the buoyancy of water can block pain signals, by acting on thermal and mechanoreceptor receptors and increasing blood flow. There is also the mental relaxation associated with hydrotherapy that promotes pain improvement (Bender 2005), and underwater exercises improve aggravating locomotor factors and restore muscle pump (Forestier 2014). It has been shown that calf strengthening improves muscle endurance, and may even restore proper muscle pump function, with increased ejection fraction and reduced residual fraction (Caggiati 2018).

The largest RCT in the field to date has shown that balneotherapy provides a significant improvement in clinical symptoms and quality of life for patients with advanced CVI, for at least one year of follow-up (Carpentier 2014).

Why it is important to do this review

There is a high prevalence of varicose veins and other signs of CVI, like oedema, skin changes, or venous ulcerations, which result in a large financial burden on the health systems (Gloviczki 2011). Balneotherapy is a relatively cheap and efficient way to deliver physical therapy (Klick 2008). Balneotherapy, either alone or combined with usual care, may provide a significant improvement in the quality of life of patients, when compared with usual care alone. This treatment is usually well tolerated, especially for those who do not consistently wear their compression stockings, or those for whom there is no surgical solution (Forestier 2014). This type of therapy may also be of great value in CVI in patients with few available therapeutic options (Blain 2016). This review will report on the available evidence of the effectiveness and safety of balneotherapy, to allow healthcare professionals and consumers to make informed decisions on treatment methods for CVI, and will highlight any uncertainties about this treatment.

OBJECTIVES

To asses the effects and safety of balneotherapy for the treatment of patients with chronic venous insufficiency (CVI).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised and quasi-randomised controlled trials that compare balneotherapy for CVI with other types of treatment.

Types of participants

We will include all participants, who are at least 18 years of age, diagnosed with CVI (primary or post-thrombotic), with evidence of venous incompetence, demonstrated by ultrasound duplex examination, with at least a significant reflux.

We will exclude participants with contra-indication to spa treatment (cardiac or renal failure, immunodeficiency, psychiatric disorders, limited walking ability). We will also exclude participants with oedema of non-venous origin (clinical lymphoedema, cardiac failure, hypoalbuminaemia), symptomatic neurological diseases of the lower limbs (neurogenic pain or abnormal neurological examination of the lower limbs), or with significant peripheral arterial disease (ankle-brachial index (ABI) < 0.90).

Types of interventions

We will include studies that evaluate balneotherapy treatment, defined as bathing in natural mineral or thermal waters. Because of its many treatment options, combinations, and duration, there is currently no detailed definition of balneotherapy. Therefore, we will include any type of balneotherapy treatment described by the study authors. We will include studies that compare balneotherapy against placebo or no treatment, and compare treatment methods against each other. We will include comparisons with other treatments such as:

- placebo or no treatment;
- compression therapy (including elastocompression, mechanical compression);
- phlebotonic drugs (including flavonoids or synthetic products in any dose or frequency);
- any other treatment.

Treatments may be used in combination, as long as the comparison treatments are balanced across groups and balneotherapy is the differentiating treatment.

Types of outcome measures

Primary outcomes

- Disease severity signs and symptoms score (measured using any validated instrument, such as the Venous Clinical Severity Score (VCSS (Rutherford 2000)). See Table 1.
- Health-related quality of life (QoL, measured using any validated instrument, such as the Chronic Venous Insufficiency Questionnaire 2 (CVIQ2) or EuroQol 5D (Brooks 1996; Launois 1996))
- Adverse events of treatment (including palpitation, superficial thrombosis, infection or erysipelas, risk of falling)

Secondary outcomes

- Pain (measured using validated visual analogue scales (VAS); patient grades pain from no discomfort at 0.0, to unbearable at 10.0)
- Oedema (measured by validated scales, such as VAS, perimeter, or volume of the leg)
- Incidence of leg ulcer
- Skin pigmentation changes (measured using validated methods, including skin chromametry)

We will report the time points presented in the studies.

Search methods for identification of studies

We will apply no restrictions on language of publication.

Electronic searches

The Cochrane Vascular Information Specialist (CIS) will search the following databases for relevant trials:

- The Cochrane Vascular Specialised Register;
- The Cochrane Central Register of Controlled Trials (CENTRAL) via The Cochrane Register of Studies Online.

See Appendix 2 for details of the search strategy, which will be used to search CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS, and is constructed from weekly electronic searches of MEDLINE, Embase, CINAHL, and AMED, and through handsearching relevant journals. The full list of the databases, journals, and conference proceedings that have been searched, as well as the search strategies used, are described in the Specialised Register section of the Cochrane Vascular module in the Cochrane Library.

The CIS will search the following trial registries for details of ongoing and unpublished studies:

- ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch)

The review authors will search LILACS (Latin American and Caribbean Health Science Information database) and IBECS (Indice Bibliograf´ fico Espan˜ ol de Ciencias de la Salud), both at lilacs.bvsalud.org/. See Appendix 3 for details of the search strategy that we will use. We will not use a filter, but will select the RCTs manually in the LILACS and IBECS databases. Three review authors (MAMS, LCUN, and FMJ) configured this search strategy. The review authors, in collaboration with the Cochrane Brasil Information Specialist, will search these databases.

Searching other resources

We will check the bibliographies of included trials for further references to relevant trials. We will contact specialists in the field, manufacturers, and authors of the included trials for any possible unpublished data.

Data collection and analysis

Selection of studies

Two review authors (MAMS, LCUN) will independently review studies retrieved by the search strategies and assess if the trials meet the selection criteria, based on title, abstract, or both. Both review authors will independently assess selected studies for complete analysis. We will resolve conflicts through discussion, and if necessary, by involving a third review author, who will have the final vote (LLC or FMJ). All studies without an abstract will be reviewed in full text. Studies only published as an abstract will be

included if sufficient data are available to determine study eligibility. If necessary, we will contact the authors of the abstract for further information. We will present a PRISMA flow diagram to show the process of trial selection.

Data extraction and management

Two review authors (MAMS and LCUN) will independently extract the data, transcribing it onto pre-established collection forms. We will resolve disagreements by discussion within the review team. We will collect the following information:

- Characteristics of the study: details of the publication (e.g. year, country, authors, journal), study design, population data (e.g. age, comorbidities, CEAP classification of venous disease, duration of disease, history of previous treatments), details of intervention (e.g. type of therapy, duration of therapy), adverse events (palpitation, superficial thrombosis, erysipelas, risk of falling), number of participants allocated to each treatment group, duration of follow-up, cost of treatment
- Results: outcomes measured, time points at which outcomes were assessed, health-related QoL measurement (e.g. Chronic Venous Insufficiency Questionnaire 2 or EuroQol 5D)

Assessment of risk of bias in included studies

Two review authors (LLC and FMJ) will independently assess all the included trials using Cochrane's 'Risk of bias' tool, described in Section 8.5 of the *Cochrane Handbook for Systematic Reviews of interventions* (Higgins 2011). We will evaluate the following sources of risk: random sequence generation, adequate concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and any other bias. We will assess each item according to what was reported in each individual study, and decide if they are at high, low, or unclear risk of bias. We plan to contact the study author(s) to seek clarification in cases of uncertainty over methodology or data.

Measures of treatment effect

For binary outcomes (leg ulcer incidence and adverse events), we will present the results using risk ratio (RR) with 95% confidence intervals (CI). For the continuous outcomes (disease severity, health-related QoL, pain, oedema, skin pigmentation) we will present the results as a mean difference (MD) with 95% CI. If studies have not used the same scales, we will present the results as a standardised mean difference (SMD) with 95% CI.

Unit of analysis issues

We will consider each participant as the unit of analysis. For trials that consider multiple interventions in the same group, we will only analyse the data of interest.

Dealing with missing data

We will note partial and incomplete data on the data collection form, and take this into account when assessing the overall quality of the study. We will also try to contact the study authors if this occurs. We will report missing data in the 'Characteristics of included studies' tables of the review, and we will use intention-to-treat analysis.

Assessment of heterogeneity

We will quantify inconsistency among the pooled estimates using the I^2 statistic, which examines the percentage of total variation across trials due to heterogeneity rather than variation due to chance (Higgins 2011). We will interpret the thresholds for the I^2 statistic as follows: less than 30% = low heterogeneity, 30% to 60% = moderate heterogeneity, 60% to 90% = substantial heterogeneity, and more than 90% = considerable heterogeneity (Higgins 2011). If studies differ methodologically and clinically, it may be preferable not to pool the results.

Assessment of reporting biases

We will assess the presence of publication bias and other reporting bias using funnel plots, if more than 10 studies are included in the meta-analysis. If asymmetry is present, we will explore possible causes, including publication bias, poor methodological quality, and true heterogeneity (Higgins 2011).

Data synthesis

We will carry out statistical analysis using Review Manager 5 software (RevMan 2014). We will use a random-effects model to synthesize the data because of the complexity of the intervention and differences in existing balneotherapy regimens. We will use risk ratio (RR) if the data are dichotomous, or a difference between means if the data are continuous. If it is not possible to pool data using a meta-analysis, we will describe the data narratively.

Subgroup analysis and investigation of heterogeneity

If possible, we will perform subgroup analyses to consider the following.

- Age
- Gender
- Severity of CVI
- Duration of treatment
- Diabetes
- Obesity
- Osteomuscular diseases
- Post-thrombotic syndrome

Sensitivity analysis

If sufficient studies are identified, we will conduct sensitivity analysis, depending on the study characteristics identified during the review process. We will perform the analysis based on allocation concealment (high, low, or unclear risk of bias), and blinding of outcome assessment (high, low, or unclear risk of bias). In addition, we will carry out analyses excluding those trials that are judged to be of high risk of bias for all domains (Higgins 2011).

'Summary of findings' table

Using GRADEpro GDT software, we will prepare 'Summary of findings' tables to present the key information for balneotherapy versus other treatments in participants with CVI (GRADEpro GDT). We will create one table for each treatment comparison (compression, phlebotonics, etc). We will include the following outcomes in each table.

- Disease severity signs and symptoms
- Health-related QoL
- Adverse events of treatment
- Pain
- Oedema
- Incidence of leg ulcer
- Skin pigmentation changes

We will assess the quality of the evidence for each outcome as high, moderate, low, or very low, based on the criteria of risk of bias, inconsistency, indirectness, imprecision, and publication bias, using the GRADE approach (GRADE 2004). We will base this table on methods described in Chapter 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions*, and justify any departures from the standard methods (GRADE 2004; Higgins 2011). We have included an example of a 'Summary of findings' table for the comparison of 'Balneotherapy versus elastocompression for chronic venous insufficiency'. See Table 2.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Venous Clinical Severity Score (VCSS)

Clinical descriptor	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Pain	None	Occasional	Daily not limiting	Daily limiting
Varicose veins	None	Few	Calf or thigh	Calf and thigh
Venous oedema	None	Foot and ankle	Below knee	Knee and above
Skin pigmentation	None	Limited perimalleolar	Diffuse lower 1/3 calf	Wider above lower 1/3 calf
Inflammation	None	Limited perimalleolar	Diffuse lower 1/3 calf	Wider above lower 1/3 calf
Induration	None	Limited perimalleolar	Diffuse lower 1/3 calf	Wider above lower 1/3 calf
Number of active ulcers	None	1	2	3 or more
Ulcer duration	None	< 3 month	3 to 12 month	> 1 year
Active ulcer size	None	< 2 cm	2 to 6 cm	> 6 cm

Table 1. Venous Clinical Severity Score (VCSS) (*Continued*)

Compression therapy	None	Intermitent	Most days	Fully comply

Table 2. Balneotherapy versus elastocompression for chronic venous insufficiency

Balneotherapy versus elastocompression for chronic venous insufficiency						
Patient or population: people with CVI **Settings:** outpatient (secondary care) **Intervention:** balneotherapy[1] **Comparison:** elastocompression						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Elastocompression	**Balneotherapy**				
Disease severity signs and symptoms (VCSS) (follow-up]	The mean [outcome] ranged across control groups from [value][measure]	The mean [outcome] in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]		[value] ([value])	⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
Health-related QoL [Chronic Venous Insufficiency Questionnaire 2 or EuroQol 5D] [follow-up]	The mean [outcome] ranged across control groups from [value][measure]	The mean [outcome] in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]		[value] ([value])	⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
Adverse events of treatment [follow-up]	[value] per 1000	[value] per 1000 ([value] to [value])		[value] ([value])	⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	

Table 2. Balneotherapy versus elastocompression for chronic venous insufficiency (*Continued*)

Pain (VAS 0 to 10. No discomfort (0.0) , to unbearable (10.0) [follow-up]	The mean pain ranged across control groups from [value][measure]	The mean pain in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]		[value] ([value])	⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
Oedema [outcome for assessing amount of oedema] [follow-up]	The mean [outcome] ranged across control groups from [value][measure]	The mean [outcome] in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]		[value] ([value])	⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
Incidence of leg ulcer [follow-up]	[value] per 1000	[value] per 1000 ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
Change in skin pigmentation [follow-up]	The mean [outcome] ranged across control groups from [value][measure]	The mean [outcome] in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]	RR [value] ([value] to [value])	[value] ([value])	⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CVI**: chronic venous insufficiency; **QoL**: quality of life: **RR:** risk ratio; **VAS**: visual analogue scale; **VCSS**: Venous Clinical Severity Score

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Balneotherapy: bathing in thermal or mineral waters

APPENDICES

Appendix 1. Glossary of terms

Term	Definition
Atrophie blanche	small smooth ivory-white areas on the skin with hyperpigmented borders and telangiectasias
Ankyloses	stiffness of a joint due to abnormal adhesion and rigidity of the bones of the joint
CEAP	comprehensive classification system developed to allow uniform diagnosis and comparison of patient populations with chronic venous disorders; created by an international ad hoc committee of the American Venous Forum in 1994. CEAP stands for clinical manifestations (C), etiological factors (E), anatomical distribution (A) and pathophysiological findings (P)
Chronic venous insufficiency	medical condition in which the veins cannot pump enough blood back to the heart
Compression therapy	application of an elastic garment around the leg
Erysipelas	acute infection, typically with a skin rash, usually on any of the legs and toes, face, arms, or fingers
Erythema	superficial reddening of the skin
Fibrosis	the thickening and scarring of connective tissue
Hyperpigmentation	increased pigmentation of an area of the skin
Lipodermatosclerosis	inflammation caused by fibrosis of subcutaneous fat
Lymphoedema	collection of fluid that causes swelling (oedema) in the arms and legs
Oedema	excess of watery fluid collecting in the tissue of the body, swelling caused when fluid leaks out of the body's capillaries
Placebo	substance or treatment with no active therapeutic effect
Superficial thrombosis	inflammatory thrombotic disorder in which a thrombus develops in a vein located near the surface of the skin

(*Continued*)

Thrombosis	local coagulation or clotting of the blood in a part of the circulatory system
Ultrasound duplex	non-invasive evaluation of blood flow through your arteries and veins
Varicose veins	gnarled, enlarged veins
Vascular	relating to blood vessel
Venoactive drugs	heterogeneous group of medicinal products, which have effects on symptoms related to chronic venous disease
Venous	relating to a vein
Venous eczema	long-term skin condition that affects the lower legs

Appendix 2. CENTRAL search strategy

#1 MESH DESCRIPTOR Venous Insufficiency EXPLODE ALL TREES 409
#2 MESH DESCRIPTOR Varicose Veins EXPLODE ALL TREES 814
#3 MESH DESCRIPTOR Saphenous Vein EXPLODE ALL TREES 636
#4 ((varicos* near3 (vein* or veno*))):TI,AB,KY 884
#5 ((tortu* near3 (vein* or veno*))):TI,AB,KY 9
#6 ((incomp* near3 (vein* or veno* or saphenous or valv*))):TI,AB,KY 99
#7 ((insuffic* near3 (vein* or veno* or saphenous))):TI,AB,KY 164
#8 (((saphenous or vein* or veno*) near3 reflux)):TI,AB,KY 165
#9 GSV:TI,AB,KY 145
#10 CVI:TI,AB,KY 164
#11 CVD:TI,AB,KY 2936
#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 5112
#13 MESH DESCRIPTOR Hydrotherapy EXPLODE ALL TREES 1387
#14 MESH DESCRIPTOR Balneology EXPLODE ALL TREES 493
#15 aqua*:TI,AB,KY 1035
#16 Balneo*:TI,AB,KY 294
#17 Bath:TI,AB,KY 1501
#18 bathe*:TI,AB,KY 107
#19 bathing:TI,AB,KY 410
#20 Baths:TI,AB,KY 490
#21 Hydrotherap*:TI,AB,KY 310
#22 spa:TI,AB,KY 666
#23 thalasso*:TI,AB,KY 8
#24 water:TI,AB,KY 16567
#25 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 20622
#26 #12 AND #25 93

Appendix 3. LILACS and BECS search strategy

(mh: (hydrotherapy) OR mh: (hidroterapia) OR (bath* whirlpool) OR (hydrotherapies) OR (e02.779.492*) OR (e02.831.535.492*) OR (hp3.018.148*) OR mh: (balneology) OR mh: (balneología) mh: (balneologia) OR (balneotherapy) OR (e02.056*) OR (hp3.018.091*) OR mh: (physical therapy modalities) OR mh: (modalidades de fisioterapia) OR (modalidades de fisioterapia) OR (neurological physiotherapy) OR (neurophysiotherapy) OR (physical therapy techniques) OR (modalit* physical therapy) OR (physical therapy technique*) OR (physiotherap* techniques) OR (physiotherapy neurological) OR (e02.779*) OR (e02.831.535*)) AND (mh: (venous insufficiency) OR mh: (insuficiencia venosa) OR mh: (insuficiência venosa) OR (insufficienc* venous) OR (c14.907.952*) OR mh: (varicose veins) OR mh: (várices) OR mh: (varizes) OR (varix) OR (varicose vein*) OR (varices) OR (c14.907.927*) OR mh: (edema) OR (anasarca) OR (dropsy) OR (hydrops) OR (c23.888.277*) OR mh: (venous thrombosis) OR mh: (trombosis de la vena) OR mh: (trombose venosa) OR (deep venous thrombosis) OR (deep-vein thrombos*) OR (deep-venous thrombos*) OR (deep vein thrombos*) OR (deep venous thrombos*) OR (phlebothrombos*) OR (thrombos* venous) OR (c14.907.355.830.925*) OR mh: (postthrombotic syndrome) OR mh: (síndrome postrombótico) mh: (síndrome pós-trombótica) OR (venous stasis syndrome) OR (syndrome postthrombotic) OR (syndrome venous stasis) OR (c14.907.355.830.925.462*) OR (c14.907.952.880*) OR mh: (venous thromboembolism) OR mh: (tromboembolia venosa) OR mh: (tromboembolia venosa) OR (thromboembolism venous) OR (c14.907.355.590.700*) OR mh: (embolism AND thrombosis) OR mh: (embolia y trombosis) OR mh: (embolia e trombose) OR (thrombosis AND embolism) OR (c14.907.355*)) AND (instance:"regional") AND (db:("LILACS" OR "IBECS"))

CONTRIBUTIONS OF AUTHORS

MAMS: draft protocol, acquire trial reports, trial selection, data extraction, data analysis, data interpretation, draft review, and future review updates, guarantor of the review

LCUN: draft protocol, trial selection, data extraction, data analysis, data interpretation, draft review, and future review updates

LLC: draft protocol, trial selection, data extraction, data analysis, data interpretation, draft review, and future review updates

FM: draft protocol, trial selection, data extraction, data analysis, data interpretation, draft review, and future review updates

DECLARATIONS OF INTEREST

MAMS: none known

LCUN: none known

LLC: none known

FM: none known

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NOTES

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