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[Intervention Protocol]

Sulodexide for treating venous leg ulcers

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of sulodexide for treating venous leg ulcers.

BACKGROUND

Description of the condition

Leg ulcers are usually defined as a loss of skin on the lower limb that takes more than six weeks to heal (Nelson 2008). Leg ulceration is a common chronic disease and the prevalence ranges from 0.62 to five per 1000 people, varying from country to country, for example, the prevalence of leg ulcers is 0.62/1000 in Australia (Baker 1991), 1/1000 in China (Fu 1998), 1.6/1000 in Sweden (Nelzen 1994), 1.5 to 3/1000 in the United Kingdom (NHS CRD 1997), and 5/1000 for the proportion of the population in the United States that is over 20 years of age (Coon 1973). Moreover, leg ulcer prevalence increases with age, rising to a peak prevalence between 60 and 80 years old, with women suffering from ulcers about 1.6 times more frequently than men (Valencia 2001). In addition, high risk factors for leg ulcers include prolonged standing (McCulloch 2001), obesity, a sedentary lifestyle and family history (Beebe-Dimmer 2005).

Approximately, 80% to 85% of all leg ulcers occur as a result of venous diseases (Simon 2004). Venous leg ulcers, also known as varicose ulcers or stasis ulcers, are a chronic and recurrent disease. The estimated recurrence rate for healed ulcers ranges from 26% to 69% in the first year (Mayer 1994; Franks 1995), rising to 75% after two years (Mayer 1994). Leg ulcers have become a big financial burden to both patients and health services (Hareendran 2005). The annual expenditure on leg ulceration is GBP 230 to 400 million (1991 prices) according to the National Health Service in the United Kingdom (Bosanquet 1992), and the cost is estimated to be as high as USD 1.9 to 2.5 billion per year in the United States (Valencia 2001). Moreover, leg ulcers can have a serious impact on patients' quality of life (González-Consuegra 2011; Herberger 2011).

Venous leg ulcers are strongly associated with chronic venous insufficiency (CVI) (White 2005). The venous blood flow system in the lower extremity consists of the deep veins, superficial veins and perforator veins, all of which are equipped with one-way open valves to prevent reflux (flow in the opposite direction). Deep veins are distributed within the calf muscle, and possess high blood pressure due to contraction of the calf muscle. By contrast, blood pressure within the superficial veins is lower. Perforator veins communicate between the deep and superficial veins. Normally, the

valves of the perforator veins close when the calf muscle contracts in order to separate the superficial veins from the high pressure of the deep veins. The valves open while the calf muscle relaxes to let blood from the superficial veins flow through the perforator veins into the deep veins. Abnormally, CVI occurs when the normal venous system is disturbed by diseases of the venous system (incompetent vein valves, loss of vein wall elasticity, lesions obstructing the venous tract, etc.) or failure of the calf muscle pumping system (Valencia 2001; White 2005), which lead to an increase in venous pressure, which is termed 'venous hypertension'. Venous hypertension is responsible for most venous disease symptoms of the leg, such as oedema (swelling due to fluid retention), lipodermatosclerosis (painful inflammation and discolouration of skin), varicose veins and ulceration. (Andreozzi 2012).

Despite the above, the pathogenic steps between venous hypertension and leg ulcers are not fully understood. One theory, called the pericapillary fibrin cuffs and fibrinolytic abnormalities hypothesis (Valencia 2001), proposes that sustained venous hypertension increases capillary permeability, leading to the leakage of fibrinogen out of the capillaries. Leaked fibrinogen polymerises to form a barrier to the diffusion of oxygen and nutrients, i.e. the 'pericapillary fibrin cuff'. The lack of oxygen and nutrients leads to local tissue cell death and the formation of ulcers (Browse 1982). Another theory, the white cell trapping hypothesis (Valencia 2001), proposes that venous hypertension decreases the pressure gradient between the arterial and venous systems of the lower extremity, leading to a reduction in the flow rate of capillary blood that results in white blood cells (leukocytes) becoming trapped. These white blood cells can form a direct physical barrier, and also release certain mediators (such as collagenase, elastase, cytokines, free radicals and chemotactic factors, etc.), resulting in an increase in capillary permeability, leakage of fibrinogen, and the inflammatory reaction that leads to ulceration (Pascarella 2005).

As there is no gold standard for the diagnosis of venous leg ulcers, it is difficult to apply a standard definition. Nonetheless, it is important to distinguish the origin of a leg ulcer i.e. whether it is due to venous, arterial or neuropathic disease, or any other causes (Velasco 2011). Arterial leg ulcers can be excluded through measuring the ankle-brachial pressure index (ABPI) by doppler ultrasonography. An ABPI less than or equal to 0.5 indicates that leg ulcers are caused by arterial disease. Neuropathic ulcers are more common in patients suffering from diabetes mellitus (Valencia 2001).

Description of the intervention

The goals of interventions for venous leg ulcers include promoting ulcer healing, reducing recurrence of ulcers, improving quality of life and reducing adverse effects (De Araujo 2003; Nelson 2008). Among the variety of types of therapy, compression therapy has emerged as the standard treatment for venous leg ulcers (NHS CRD 1997; Nelson 2008; O'Meara 2009), however, it usually takes a long time for ulcer healing (Erickson 1995), and compression is not suitable for patients with arterial disease (NHS CRD 1997; Nelson 2008). Adjuvant (additional) drug therapies have also been studied (e.g. pentoxifylline (Jull 2011), flavonoids (Scallon 2013), and aspirin (Magolbo 2011)). Sulodexide has also been suggested as a potential candidate for adjuvant treatment of venous leg ulcers (Nelson 2008).

Sulodexide is a highly purified glycosaminoglycan (GAG) consisting of 80% fast-moving heparin (FMH) and 20% dermatan sulphate (DS). The FMH (7000 Da) is composed of unfractionated heparin and a fraction with a lower electrophoretic mobility. The DS (25,000 Da) is a polydisperse polysaccharide (Cosmi 2003). Compared with heparin, sulodexide shows a longer half-life and lower risk of haemorrhage (Lasierra-Cirujeda 2010).

Sulodexide is primarily used in patients with thrombotic risk diseases, and is administrated either orally or parenterally (e.g. via infusion). Scondotto et al first studied sulodexide clinically for the treatment of venous leg ulcers (Scondotto 1999), followed by Coccheri et al (Coccheri 2002), and Kucharzewski et al (Kucharzewski 2003).

How the intervention might work

Sulodexide has good antithrombotic and profibrinolytic activities, and also an anti-inflammatory effect (Andreozzi 2012).

Sulodexide has an antithrombotic effect by inhibiting thrombin activity and thrombin formation (Cosmi 2003). Thrombin is an essential part of the coagulation (blood clotting) system as it helps to convert fibrinogen to fibrin. Sulodexide has a positive effect on various blood components that inhibit thrombin activity and also has a negative effect on blood components that promote the conversion of prothrombin into thrombin.

Sulodexide exerts fibrinolytic activity by promoting the conversion of plasminogen to plasmin, which results in fibrinolysis (the breaking up of fibrin).

Moreover, recent studies demonstrate sulodexide has anti-inflammatory activity (Andreozzi 2012). Karoń 2007 demonstrated that systemic (whole body) administration of sulodexide reduced intraperitoneal and vascular inflammation in rats. (Ciszewicz 2009) demonstrated that sulodexide exerts an anti-inflammatory effect in human endothelial cells by suppressing the generation of oxygen-derived free radicals, and the release of monocyte chemotactic protein-1 (MCP-1) and interleukin-6 (IL-6).

Why it is important to do this review

Venous leg ulcers are a common, chronic, recurrent disease. Although the activity of sulodexide has been investigated in clinical trials treating venous leg ulcers, its role has not been conclusively defined, and it would be helpful to do so.

OBJECTIVES

To assess the efficacy and safety of sulodexide for treating venous leg ulcers.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including cluster-randomised trials and randomised controlled cross-over trials, either published or unpublished. Studies using quasi-randomisation will be excluded.

Types of participants

People of any age, gender, and in any care setting, described as having a venous leg ulcer will be eligible for inclusion. As a minimum, the included participants must be described as having leg ulcers caused by venous diseases.

Types of interventions

Oral or parenteral administration of sulodexide (any strength and over any period of administration) compared with placebo or any other drug therapy (such as pentoxifylline, flavonoids, aspirin, etc.), with or without compression therapy.

Types of outcome measures

Primary outcomes

- Proportion of ulcers completely healed during follow up.
- Time to complete ulcer healing.
- Percentage, or absolute, change in ulcer size.

Secondary outcomes

- Ulcer recurrence.
- All reported adverse events, such as bleeding, allergic reaction, injection site pain, gastrointestinal reaction, etc..
- Health-related quality of life (measured using a validated standardised generic questionnaire such as EQ-5D (Herdman 2011), SF-36 (Ware 2000), or validated disease-specific questionnaire (Augustin 1997)).
- Direct costs.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases to identify relevant RCTs:

- The Cochrane Wounds Group Specialised Register (latest version).
- The Cochrane Central Register of Controlled Trials (CENTRAL) (latest issue).
- Ovid MEDLINE (1946 to present).
- Ovid EMBASE (1974 to present).
- CINAHL (1982 to present).
- Chinese Biomedical Literature Database (CBM) (1978 to present).
- China National Knowledge Infrastructure Database (CNKI) (1979 to present).
- Wan Fang database (1986 to present).
- VIP Database (1989 to present).

We will use the following provisional search strategy in The Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor Leg Ulcer explode all trees
#2 ((varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (stasis NEXT ulcer*) or (crural NEXT ulcer*) or “ulcus cruris” or “ulcer cruris”):ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Glycosaminoglycans explode all trees
#5 (sulodexide or mucopolysaccharide* or glycosaminoglycan* or vessel or aterina or luzone or (glucuronyl* NEAR/1 sulfate) or 3-glucosaminoglycan or KRX-101):ti,ab,kw
#6 (#4 OR #5)
#7 (#3 AND #6)
We will adapt this strategy to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL. We will combine the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We will combine the EMBASE search with the Ovid EMBASE filter developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2012). We will also translate the search strategy appropriately for searching each Chinese database. We will not restrict studies with respect to language, date of publication or study setting.
We will search the following clinical trials registries:

- ClinicalTrial.gov (http://clinicaltrials.gov/).
- International Standard Randomised Controlled Trial Number Register (ISRCTN) (http://www.controlled-trials.com/isrctn/).
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/).

- Chinese Clinical Trial Registry (ChiCTR) (http://www.chictr.org/cn/).

Searching other resources

We will search the references listed in relevant trials and reviews to identify any further relevant RCTs.

Data collection and analysis

Selection of studies

We will use EndNote X3 software to merge retrieved reports of each database and remove duplicate records of the same study. Two review authors (BW, JL) will assess titles and abstracts of studies independently to exclude obviously irrelevant reports. We will retrieve full text copies of all potentially eligible reports, and review them in the light of the inclusion criteria. Final decisions on the included studies will be made through cross-checking the results of the two review authors (BW, JL), and a third review author (MY) will be consulted if there are any disagreements. Where we identify multiple reports of the same trial, we will extract the maximum amount of data from the multiple reports and identify one report as the primary reference. We will set out a study flow diagram as recommended by the PRISMA statement to illustrate the process of screening and selecting studies for inclusion in the review (Liberati 2009).

Data extraction and management

We will undertake data extraction based on the data extraction sheet provided by the Cochrane Wounds Group, which will include the following information: general data (authors, publication year, contact information, etc.), baseline data (participants' number, age, gender, etc.), risk of bias assessment information (randomisation, allocation concealment, blinding, incomplete outcome data, etc.), interventions, duration of follow up, outcome measures and results. We plan to contact the study authors for more information, if necessary.

Independently, two review authors (BW, JL) will extract and manage data from all included trials. Disagreements will be resolved by discussion. If these authors fail to reach an agreement, a third review author (MY) will act as arbiter.

Assessment of risk of bias in included studies

Risk of bias will be assessed using the methods recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook) (Higgins 2011). The following seven items will be evaluated independently for each study by two review authors (BW, MY): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. We will judge risk of bias for each item as 'Low risk', 'High risk' and 'Unclear risk' following the assessment criteria recommended by the Cochrane Handbook (Appendix 1). Finally, we will present a 'Risk of bias summary' and 'Risk of bias' figures to present an assessment of risk of bias.

Measures of treatment effect

For dichotomous outcomes (e.g. proportion of ulcers completely healed), we will present risk ratio (RR) with 95% confidence interval (CI) for each individual trial. For continuous outcomes (e.g. percentage change in ulcer size), we will use mean difference (MD) with 95% CI for individual trials; Where the same outcome is measured in a variety of ways among studies, we will use standardised mean differences (SMD) with 95% CI. We will use a fixed-effect model to combine studies if no significant heterogeneity exists, otherwise, a random-effects model will be applied. For time-to-event data (e.g. time to complete ulcer healing), estimates of hazard ratio (HR) and 95% CI as presented in the trial reports, will be converted into the log rank observed minus expected events and variance of the log rank statistic, and these estimates will be pooled using a fixed-effect model (random-effects model is not available for this analysis) (Deeks 2011).

Unit of analysis issues

We will consider individual participants as the unit of analysis. Any cluster-randomised trials identified, if possible, will be re-analysed by calculating the effective sample sizes with the intra-cluster coefficient (ICC) estimated externally from similar studies (Deeks 2011). If the same outcomes were reported at different time points, we will first perform an overall analysis, pooling all the included studies, if there are sufficient RCTs, we will perform subgroup analysis of different periods of follow up.

Dealing with missing data

We will attempt to contact the original study authors when essential data are missing. If no reply is received after eight weeks, we will assume the missing participants had both positive and negative outcomes (e.g. missing participants assumed for ulcers healed and ulcers not healed), and will undertake an analysis based on these assumptions (best case / worst case scenario) respectively, performing a sensitivity analysis.

Assessment of heterogeneity

Firstly, if clinical diversity exists between the trials (e.g. ulcers of different severity, different types of interventions, or different durations of follow up), we will not combine data from these trials and will present a narrative summary. Secondly, for clinically homogeneous (similar) studies, we will perform a Chi^2 test, with P values less than 0.1 indicating significant statistical heterogeneity. In order to quantify heterogeneity not due to chance, I^2 statistics will be used (Higgins 2011). A rough guide for the interpretation of I^2 is as follows: 0% to 40% represents heterogeneity that might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% represents considerable heterogeneity (Deeks 2011).

Assessment of reporting biases

We will perform a comprehensive search for eligible RCTs to minimise reporting bias. If more than 10 studies are included, we will use funnel plots to assess publication bias (Sterne 2011).

Data synthesis

We will analyse the data using RevMan 5.1 software provided by the Cochrane Collaboration. We will use a fixed-effect model for meta-analysis in the absence of clinical, methodological and statistical heterogeneity. If the I^2 statistic is greater than zero, additionally, we will apply a random-effects model to see whether the conclusions differ, and any difference will be noted. If pooling is not possible or appropriate, we will present a narrative summary (Deeks 2011).

Subgroup analysis and investigation of heterogeneity

If clinical heterogeneity is investigated and there are sufficient RCTs included, we will conduct subgroup analyses as follows:

- Difference in severity of leg ulcers, determined by size (> 5 cm or ≦ 5 cm) or ulcer duration (> 6 months or ≦ 6 months) at baseline.
- Different types of interventions, determined by the type of control group (placebo or other therapies) or combination of compression therapy (with or without compression).
- Different durations of follow up.

Sensitivity analysis

If sufficient RCTs are included, we will perform a sensitivity analysis for the primary outcomes to investigate the robustness of findings. Sensitivity analysis will be conducted by comparing meta-analysis results of:

- RCTs with low risk of bias (adequate sequence generation, adequate allocation concealment and an adequate method of outcome assessor blinding) compared with all included RCTs.
- Assumption that missing participants had a positive outcome versus a negative outcome.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Criteria for judging risk of bias

Random sequence generation

'Low risk' of bias

The investigators describe a random component in the sequence generation process such as:

- Referring to a random number table.
- Using a computer random number generator.
- Coin tossing.
- Shuffling cards or envelopes.

- Throwing dice.
- Drawing of lots.
- Minimization.

'High risk' of bias

The investigators describe a non-random component in the sequence generation process, for example:

- Sequence generated by odd or even date of birth.
- Sequence generated by some rule based on date (or day) of admission.
- Sequence generated by some rule based on hospital or clinic record number.
- Allocation by judgement of the clinician.
- Allocation by preference of the participant.
- Allocation based on the results of a laboratory test or a series of tests.
- Allocation by availability of the intervention.

'Unclear risk' of bias

Insufficient information about the sequence generation process to permit judgement of low risk or high risk to be made.

Allocation concealment

'Low risk' of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

- Central allocation (including telephone, web-based and pharmacy-controlled randomisation).
- Sequentially numbered drug containers of identical appearance.
- Sequentially numbered, opaque, sealed envelopes.

'High risk' of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:

- Using an open random allocation schedule (e.g. a list of random numbers).
- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered).
- Alternation or rotation.
- Date of birth.
- Case record number.
- Any other explicitly unconcealed procedure.

'Unclear risk' of bias

Insufficient information to permit judgement of low risk or high risk to be made. This is usually the case if the method of concealment is not described, or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

Blinding of participants and personnel

'Low risk' of bias

Either of the following:

- No blinding, or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

'High risk' of bias

Either of the following:

- No blinding, or incomplete blinding, and the outcome is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

'Unclear risk' of bias

Either of the following:

- Insufficient information available to permit judgement of low risk or high risk.
- The study did not address this outcome.

Blinding of outcome assessment

'Low risk' of bias

Either of the following:

- No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding.
- Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

'High risk' of bias

Either of the following:

- No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding.
- Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

'Unclear risk' of bias

Either of the following:

- Insufficient information available to permit judgement of low risk or high risk to be made.
- The study did not address this outcome.

Incomplete outcome data

'Low risk' of bias

Any one of the following:

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).

- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

'High risk' of bias

Any one of the following:
- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

'Unclear risk' of bias

Any one of the following:
- Insufficient reporting of attrition/exclusions to permit judgement of low risk or high risk (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

Selective reporting

'Low risk' of bias

Either of the following:
- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

'High risk' of bias

Any one of the following:
- Not all of the study's pre-specified primary outcomes have been reported.
- One, or more, primary outcome is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
- One, or more, reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One, or more, outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

'Unclear risk' of bias

Insufficient information to permit judgement of low risk or high risk. It is likely that the majority of studies will fall into this category.

Other potential sources of bias

'Low risk' of bias

The study appears to be free of other sources of bias.

'High risk' of bias

There is at least one important risk of bias. For example, the study:

- Had a potential source of bias related to the specific study design used.
- Has been claimed to have been fraudulent.
- Had some other problem.

'Unclear risk' of bias

There may be a risk of bias, but there is either:

- Insufficient information to assess whether an important risk of bias exists.
- Insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

Bin Wu conceived the review question, developed the protocol, co-ordinated development, completed the first draft, performed part of the writing and editing of the protocol, advised on the protocol and approved final version prior to submission.

Jing Lu developed the protocol and co-ordinated development, completed the first draft, performed part of the writing and editing of the protocol, advised on the protocol and approved the final version prior to submission.

Ming Yang co-ordinated the protocol development, made an intellectual contribution, advised on part of the protocol and approved the final version prior to submission.

Ting Xu conceived the review question, made an intellectual contribution, advised on the protocol and approved the final version prior to submission.C

Contributions of editorial base:

Nicky Cullum: edited the protocol; advised on methodology, interpretation and protocol content.
Joan Webster, Editor: approved the protocol for publication.
Sally Bell-Syer: coordinated the editorial process. Advised on methodology, interpretation and content. Edited the protocol.
Ruth Foxlee: designed the search strategy and edited the search methods section.

DECLARATIONS OF INTEREST

None known.

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